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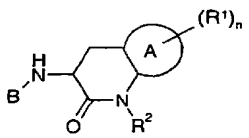
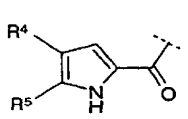
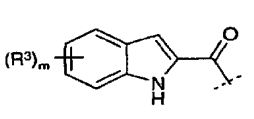
(54) Title: HETEROCYCLIC AMIDE DERIVATIVES WHICH POSSES GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY



(I)



(2a)



(2b)

(57) Abstract: Heterocyclic amides of formula (1) wherein: B is selected from R4 and R 5 together are either -S-C(R 6)=C(R 7)_ or _C(R7)=C(R6)_S_; A is a pyridylene ring; m is 0, 1 or 2; n is 0 or 1; R 2 is for example selected from (I -4C)alkyl, hydroxy(l -4C)alkyl, dihydroxy(2-4C)alkyl and (1 -4C)alkoxy(1 -4C)alkyl. or a pharmaceutically acceptable salt possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of said heterocyclic amide derivatives, intermediates in said processes and pharmaceutical compositions containing the heterocyclic amide derivatives are described.

HETEROCYCLIC AMIDE DERIVATIVES WHICH POSSESS GLYCOGEN PHOSPHORYLASE INHIBITORY ACTIVITY

The present invention relates to heterocyclic amide derivatives, pharmaceutically acceptable salts and in-vivo hydrolysable esters thereof. These heterocyclic amides possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity and thus are potentially useful in methods of treatment of a warm-blooded animal such as man. The invention also relates to processes for the manufacture of said heterocyclic amide derivatives, intermediates in said processes, to pharmaceutical compositions containing said heterocyclic amide derivatives and to their use in the manufacture of medicaments to inhibit glycogen phosphorylase activity in a warm-blooded animal such as man.

The liver is the major organ regulating glycaemia in the post-absorptive state. Additionally, although having a smaller role in the contribution to post-prandial blood glucose levels, the response of the liver to exogenous sources of plasma glucose is key to an ability to maintain euglycaemia. An increased hepatic glucose output (HGO) is considered to play an important role in maintaining the elevated fasting plasma glucose (FPG) levels seen in type 2 diabetics; particularly those with a FPG >140mg/dl (7.8mM). (Weyer et al, (1999), J Clin Invest 104: 787-794; Clore & Blackgard (1994), Diabetes 43: 256-262; De Fronzo, R. A., et al, (1992) Diabetes Care 15; 318 - 355; Reaven, G.M. (1995) Diabetologia 38; 3-13).

Since current oral, anti-diabetic therapies fail to bring FPG levels to within the normal, non-diabetic range and since raised FPG (and glycHbA1c) levels are risk factors for both macro- (Charles, M.A. et al (1996) Lancet 348, 1657-1658; Coutinho, M. et al (1999) Diabetes Care 22; 233-240; Shaw, J.E. et al (2000) Diabetes Care 23, 34-39) and micro-vascular disease (DCCT Research Group (1993) New. Eng. J. Med. 329; 977-986); the reduction and normalisation of elevated FPG levels remains a treatment goal in type 2 DM.

It has been estimated that, after an overnight fast, 74% of HGO was derived from glycogenolysis with the remainder derived from gluconeogenic precursors (Hellerstein et al (1997) Am J Physiol, 272: E163). Glycogen phosphorylase is a key enzyme in the generation by glycogenolysis of glucose-1-phosphate, and hence glucose in liver and also in other tissues such as muscle and neuronal tissue.

Liver glycogen phosphorylase a activity is elevated in diabetic animal models including the db/db mouse and the fa/fa rat (Aiston S et al (2000). Diabetalogia 43, 589-597).

Inhibition of hepatic glycogen phosphorylase with chloroindole inhibitors (CP91149 and CP320626) has been shown to reduce both glucagon stimulated glycogenolysis and glucose output in hepatocytes (Hoover et al (1998) J Med Chem 41, 2934-8; Martin et al (1998) PNAS 95, 1776-81). Additionally, plasma glucose concentration is reduced, in a dose related manner, db/db and ob/ob mice following treatment with these compounds.

Studies in conscious dogs with glucagon challenge in the absence and presence of another glycogen phosphorylase inhibitor, Bay K 3401, also show the potential utility of such agents where there is elevated circulating levels of glucagon, as in both Type 1 and Type 2 diabetes. In the presence of Bay R 3401, hepatic glucose output and arterial plasma glucose following a glucagon challenge were reduced significantly (Shiota et al, (1997), Am J Physiol, 273: E868).

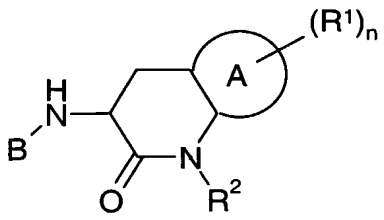
The heterocyclic amides of the present invention possess glycogen phosphorylase inhibitory activity and accordingly are expected to be of use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia and obesity, particularly type 2 diabetes.

Our patent application WO 02/20530 discloses a spectrum of active glycogen phosphorylase inhibitors, amongst which are a very limited number of dihydroquinolone containing compounds.

Our co-pending patent applications PCT/GB03/00877 and PCT/GB03/00893 disclose a variety of substituted dihydroquinolone containing glycogen phosphorylase inhibitors, generally substituted only on the nitrogen atom ("amide nitrogen"). Two examples of azadihydroquinolones (by which we mean compounds containing a nitrogen atom replacing a carbon atom of the aromatic ring, thereby forming a fused pyridine ring) are disclosed in PCT/GB03/00877, however these are not substituted on the amide nitrogen.

Surprisingly, we have found that a group of azadihydroquinolones which are substituted on the amide nitrogen and optionally substituted on the pyridine ring have physical properties (for example solubility, plasma-protein binding) and/or improved pharmacokinetic properties, and/or demonstrate greater pharmacological selectivity which are particularly beneficial for a pharmaceutical, and comparable or improved activity in comparison with that of the compounds previously disclosed.

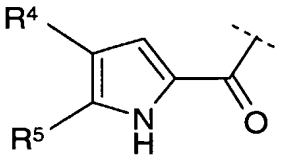
According to one aspect of the present invention there is provided a compound of formula (1):



(1)

wherein:

B is selected from



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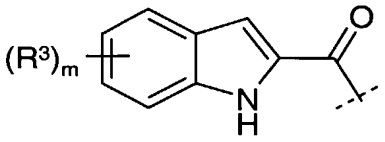
and



(2b)

R^3 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

R^4 and R^5 together are either $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

A is a pyridylene ring;

m is 0, 1 or 2;

n is 0 or 1;

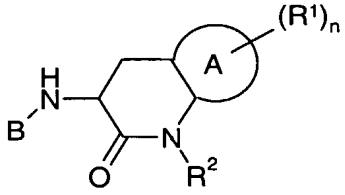
when R^1 is a substituent at the 5-position of the pyridyl ring comprising A (using the numbering system described hereinafter), R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N*,*N*-((1-4C)alkyl)$_2$carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N*,*N*-((1-4C)alkyl)$_2$sulphamoyl, -S(O)$_b$(1-4C)alkyl (wherein b is 0,1,or 2), -OS(O)$_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and $-NHSO_2$(1-4C)alkyl;

when R^1 is a substituent at the 6-, 7- or 8-position of the pyridyl ring comprising A (using the numbering system described hereinafter), R^1 is independently selected from halo, hydroxy, methyl and methoxy;

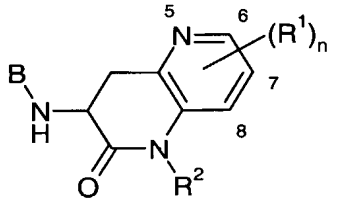
R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, –(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, -(1-4C)alkylSO_2Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl;

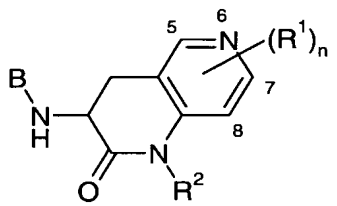
or a pharmaceutically acceptable salt or pro-drug thereof.

It is to be understood that the definition of ring A as a pyridylene ring includes all possible isomers of the pyridylene ring, except those where the nitrogen atom is at a bridgehead position. Therefore, for example, the definition of

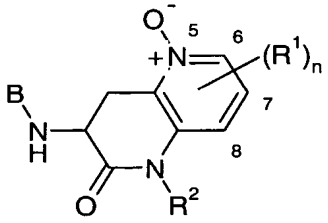


encompasses the structures:





It is to be understood that the definition of A as a pyridylene ring includes structures wherein the nitrogen atom in A has been oxidised to form the N-oxide, for example:



It will be appreciated that the numbering of the ring system according to IUPAC rules will vary according to the position of the nitrogen in the aromatic ring portion. For the sake of clarity, when the position of the substituent R^1 is referred to herein, the numbering system shown above will be used; the skilled person will understand that this is the numbering system

which applies for dihydroquinolones (that is, compounds corresponding to formula (I) where A is phenylene). However, when specific compounds are referred to by chemical name herein, such as the compounds of the Examples, the IUPAC name will be used. The compound names used in the Examples have been generated using Name" module in the ACD 5.0 program suite [Advanced Chemistry Development (Toronto, Canada)].

It is to be understood that where substituents contain two substituents on an alkyl chain, in which both are linked by a heteroatom (for example two alkoxy substituents), then these two substituents are not substituents on the same carbon atom of the alkyl chain.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pharmaceutically acceptable salt.

In another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to a pro-drug thereof. Suitable examples of pro-drugs of compounds of formula (1) are in-vivo hydrolysable esters of compounds of formula (1). Therefore in another aspect, the invention relates to compounds of formula (1) as hereinabove defined or to an in-vivo hydrolysable ester thereof.

It is to be understood that, insofar as certain of the compounds of formula (1) defined above may exist in optically active or racemic forms by virtue of one or more asymmetric carbon atoms, the invention includes in its definition any such optically active or racemic form which possesses glycogen phosphorylase inhibition activity. The synthesis of optically active forms may be carried out by standard techniques of organic chemistry well known in the art, for example by synthesis from optically active starting materials or by resolution of a racemic form. Similarly, the above-mentioned activity may be evaluated using the standard laboratory techniques referred to hereinafter.

Within the present invention it is to be understood that a compound of the formula (1) or a salt thereof may exhibit the phenomenon of tautomerism and that the formulae drawings within this specification can represent only one of the possible tautomeric forms. It is to be understood that the invention encompasses any tautomeric form which has glycogen phosphorylase inhibition activity and is not to be limited merely to any one tautomeric form utilised within the formulae drawings. The formulae drawings within this specification can represent only one of the possible tautomeric forms and it is to be understood that the specification encompasses all possible tautomeric forms of the compounds drawn not just those forms which it has been possible to show graphically herein.

It is also to be understood that certain compounds of the formula (1) and salts thereof can exist in solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which have glycogen phosphorylase inhibition activity.

It is also to be understood that certain compounds of the formula (1) may exhibit polymorphism, and that the invention encompasses all such forms which possess glycogen phosphorylase inhibition activity.

The present invention relates to the compounds of formula (1) as hereinbefore defined as well as to the salts thereof. Salts for use in pharmaceutical compositions will be pharmaceutically acceptable salts, but other salts may be useful in the production of the compounds of formula (1) and their pharmaceutically acceptable salts. Pharmaceutically acceptable salts of the invention may, for example, include acid addition salts of the compounds of formula (1) as hereinbefore defined which are sufficiently basic to form such salts. Such acid addition salts include for example salts with inorganic or organic acids affording pharmaceutically acceptable anions such as with hydrogen halides (especially hydrochloric or hydrobromic acid of which hydrochloric acid is particularly preferred) or with sulphuric or phosphoric acid, or with trifluoroacetic, citric or maleic acid. Suitable salts include hydrochlorides, hydrobromides, phosphates, sulphates, hydrogen sulphates, alkylsulphonates, arylsulphonates, acetates, benzoates, citrates, maleates, fumarates, succinates, lactates and tartrates. In addition where the compounds of formula (1) are sufficiently acidic, pharmaceutically acceptable salts may be formed with an inorganic or organic base which affords a pharmaceutically acceptable cation. Such salts with inorganic or organic bases include for example an alkali metal salt, such as a sodium or potassium salt, an alkaline earth metal salt such as a calcium or magnesium salt, an ammonium salt or for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

The compounds of the invention may be administered in the form of a pro-drug which is broken down in the human or animal body to give a compound of the invention. A prodrug may be used to alter or improve the physical and/or pharmacokinetic profile of the parent compound and can be formed when the parent compound contains a suitable group or substituent which can be derivatised to form a prodrug. Examples of pro-drugs include in-vivo hydrolysable esters of a compound of the invention or a pharmaceutically-acceptable salt thereof.

Various forms of prodrugs are known in the art, for examples see:

a) Design of Prodrugs, edited by H. Bundgaard, (Elsevier, 1985) and Methods in Enzymology, Vol. 42, p. 309-396, edited by K. Widder, *et al.* (Academic Press, 1985);

b) A Textbook of Drug Design and Development, edited by Krogsgaard-Larsen and H. Bundgaard, Chapter 5 "Design and Application of Prodrugs", by H. Bundgaard p. 113-191 (1991);

c) H. Bundgaard, Advanced Drug Delivery Reviews, 8, 1-38 (1992);

d) H. Bundgaard, *et al.*, Journal of Pharmaceutical Sciences, 77, 285 (1988); and

e) N. Kakeya, *et al.*, Chem Pharm Bull, 32, 692 (1984).

An in-vivo hydrolysable ester of a compound of formula (1) containing carboxy or hydroxy group is, for example a pharmaceutically acceptable ester which is cleaved in the human or animal body to produce the parent acid or alcohol.

Suitable pharmaceutically acceptable esters for carboxy include alkyl esters, (1-6C)alkoxymethyl esters for example methoxymethyl, (1-6C)alkanoyloxymethyl esters for example pivaloyloxymethyl, phthalidyl esters, (3-8C)cycloalkoxycarbonyloxy(1-6C)alkyl esters for example 1-cyclohexylcarbonyloxyethyl; 1,3-dioxolen-2-onylmethyl esters for example 5-methyl-1,3-dioxolen-2-onylmethyl; and (1-6C)alkoxycarbonyloxyethyl esters for example 1-methoxycarbonyloxyethyl and may be formed at any carboxy group in the compounds of this invention.

Suitable pharmaceutically-acceptable esters for hydroxy include inorganic esters such as phosphate esters (including phosphoramidic cyclic esters) and α-acyloxyalkyl ethers and related compounds which as a result of the *in-vivo* hydrolysis of the ester breakdown to give the parent hydroxy group/s. Examples of α-acyloxyalkyl ethers include acetoxymethoxy and 2,2-dimethylpropionyloxymethoxy. A selection of *in-vivo* hydrolysable ester forming groups for hydroxy include (1-10C)alkanoyl, for example acetyl; benzoyl; phenylacetyl; substituted benzoyl and phenylacetyl, (1-10C)alkoxycarbonyl (to give alkyl carbonate esters), for example ethoxycarbonyl; di-((1-4C))alkylcarbamoyl and *N*-(di-((1-4C))alkylaminoethyl)-*N*-((1-4C))alkylcarbamoyl (to give carbamates); di-((1-4C))alkylaminoacetyl and carboxyacetyl. Examples of ring substituents on phenylacetyl and benzoyl include aminomethyl, ((1-4C))alkylaminomethyl and di-(((1-4C))alkyl)aminomethyl, and morpholino or piperazino linked from a ring nitrogen atom via a methylene linking group to the 3- or 4- position of the benzoyl ring. Other interesting in-vivo hyrolysable esters include, for example, $R^A C(O)O((1-$

6C))alkyl-CO-, wherein R^A is for example, benzyloxy-((1-4C))alkyl, or phenyl). Suitable substituents on a phenyl group in such esters include, for example, 4-((1-4C))piperazino-((1-4C))alkyl, piperazino-((1-4C))alkyl and morpholino(1-4C)alkyl.

In this specification the generic term "alkyl" includes both straight-chain and branched-chain alkyl groups. However references to individual alkyl groups such as "propyl" are specific for the straight chain version only and references to individual branched-chain alkyl groups such as *t*-butyl are specific for the branched chain version only. For example, "(1-4C)alkyl" includes methyl, ethyl, propyl, isopropyl and *t*-butyl and examples of "(1-6C)alkyl" include the examples of "(1-4C)alkyl"and additionally pentyl, 2,3-dimethylpropyl, 3-methylbutyl and hexyl. An analogous convention applies to other generic terms, for example "(2-4C)alkenyl" includes vinyl, allyl and 1-propenyl and examples of "(2-6C)alkenyl" include the examples of "(2-4C)alkenyl" and additionally 1-butenyl, 2-butenyl, 3-butenyl, 2-methylbut-2-enyl, 3-methylbut-1-enyl, 1-pentenyl, 3-pentenyl and 4-hexenyl. Examples of "(2-4C)alkynyl" includes ethynyl, 1-propynyl and 2-propynyl and examples of "C_{2-6}alkynyl"include the examples of "(2-4C)alkynyl" and additionally 3-butynyl, 2-pentynyl and 1-methylpent-2-ynyl.

The term "hydroxy(1-4C)alkyl" includes hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxyisopropyl and hydroxybutyl. The term "hydroxy(1-4C)alkyl" also includes hydroxycyclopropyl and hydroxycyclobutyl. The term "hydroxyethyl" includes 1-hydroxyethyl and 2-hydroxyethyl. The term "hydroxypropyl" includes 1-hydroxypropyl, 2-hydroxypropyl and 3-hydroxypropyl and an analogous convention applies to terms such as hydroxybutyl. The term "dihydroxy(2-4C)alkyl" includes dihydroxyethyl, dihydroxypropyl, dihydroxyisopropyl and dihydroxybutyl. The term "dihydroxypropyl" includes 1,2-dihydroxypropyl, 2,3-dihydroxypropyl and 1,3-dihydroxypropyl. An analogous convention applies to terms such as dihydroxyisopropyl and dihydroxybutyl. The term dihydroxy(2-4C)alkyl is not intended to include structures which are geminally disubstituted and thereby unstable.

The term "halo" refers to fluoro, chloro, bromo and iodo. The term "dihalo(1-4C)alkyl" includes difluoromethyl and dichloromethyl. The term "trihalo(1-4C)alkyl" includes trifluoromethyl.

Examples of "(1-4C)alkoxy" include methoxy, ethoxy, propoxy and isopropoxy. Examples of "(1-6C)alkoxy" include the examples of "(1-4C)alkoxy" and additionally

butyloxy, *t*-butyloxy, pentoxy and 1,2-(methyl)$_2$propoxy. Examples of "(1-4C)alkanoyl" include formyl, acetyl and propionyl. Examples of "(1-6C)alkanoyl" include the example of "(1-4C)alkanoyl" and additionally butanoyl, pentanoyl, hexanoyl and 1,2-(methyl)$_2$propionyl. Examples of "(1-4C)alkanoyloxy" are formyloxy, acetoxy and propionoxy. Examples of "(1-6C)alkanoyloxy" include the examples of "(1-4C)alkanoyloxy" and additionally butanoyloxy, pentanoyloxy, hexanoyloxy and 1,2-(methyl)$_2$propionyloxy. Examples of "*N*-((1-4C)alkyl)amino" include methylamino and ethylamino. Examples of "*N*-((1-6C)alkyl)amino" include the examples of "*N*-((1-4C)alkyl)amino" and additionally pentylamino, hexylamino and 3-methylbutylamino. Examples of "*N,N*-((1-4C)alkyl)$_2$amino" include *N*-*N*-(methyl)$_2$amino, *N*-*N*-(ethyl)$_2$amino and *N*-ethyl-*N*-methylamino. Examples of "*N,N*-((1-6C)alkyl)$_2$amino" include the example of "*N,N*-((1-4C)alkyl)$_2$amino" and additionally *N*-methyl-*N*-pentylamino and *N,N*-(pentyl)$_2$amino. Examples of "*N*-((1-4C)alkyl)carbamoyl" are methylcarbamoyl and ethylcarbamoyl. Examples of "*N*-((1-6C)alkyl)carbamoyl" are the examples of "*N*-((1-4C)alkyl)carbamoyl"and additionally pentylcarbamoyl, hexylcarbamoyl and 1,2-(methyl)$_2$propylcarbamoyl. Examples of "*N,N*-((1-4C)alkyl)$_2$carbamoyl" are *N,N*-(methyl)$_2$carbamoyl, *N,N*-(ethyl)$_2$carbamoyl and *N*-methyl-*N*-ethylcarbamoyl. Examples of "*N,N*-((1-6C)alkyl)$_2$carbamoyl" are the examples of "*N,N*-((1-4C)alkyl)$_2$carbamoyl" and additionally *N,N*-(pentyl)$_2$carbamoyl, *N*-methyl-*N*-pentylcarbamoyl and *N*-ethyl-*N*-hexylcarbamoyl. Examples of "*N*-((1-4C)alkyl)sulphamoyl" are *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "*N*-((1-6C)alkyl)sulphamoyl" are the examples of "*N*-((1-4C)alkyl)sulphamoyl" and additionally *N*-pentylsulphamoyl, *N*-hexylsulphamoyl and 1,2-(methyl)$_2$propylsulphamoyl. Examples of "*N,N*-((1-4C)alkyl)$_2$sulphamoyl" are *N,N*-(methyl)$_2$sulphamoyl, *N,N*-(ethyl)$_2$sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "*N,N*-((1-6C)alkyl)$_2$sulphamoyl" are the examples of "*N,N*-((1-4C)alkyl)$_2$sulphamoyl" and additionally *N,N*-(pentyl)$_2$sulphamoyl, *N*-methyl-*N*-pentylsulphamoyl and *N*-ethyl-*N*-hexylsulphamoyl. Examples of "-NHSO$_2$(1-4C)alkyl" include methylsulfonylamino, ethylsulfonylamino, propylsulfonylamino, isopropylsulfonylamino and tert-butylsulfonylamino.

Examples of "-(1-4C)alkylNHSO$_2$(1-4C)alkyl" include methylsulfonylaminomethyl, ethylsulfonylaminomethyl, methylsulfonylaminoethyl, propylsulfonylaminomethyl and methylsulfonylaminopropyl. Examples of "-(1-4C)alkylSO$_2$NH(1-4C)alkyl" include methylaminosulfonylmethyl, ethylaminosulfonylethyl, ethylaminosulfonylmethyl, methylaminosulfonylpropyl and propylaminosulfonylmethyl. Examples of "-(1-

4C)alkylSO_2NHdi[(1-4C)alkyl]" include dimethylaminosulfonylmethyl, (methyl)(ethyl)aminosulfonylmethyl, diethylaminosulfonylmethyl, dimethylaminosulfonylethyl, di-isopropylaminosulfonylmethyl and dimethylaminosulfonylpropyl.

Examples of "-(1-4C)alkylNHCO(1-4C)alkyl" include methylcarbonylaminomethyl, ethylcarbonylaminomethyl, methylcarbonylaminoethyl, propylcarbonylaminomethyl and methylcarbonylaminopropyl. Examples of "-(1-4C)alkylCONH(1-4C)alkyl" include methylaminocarbonylmethyl, ethylaminocarbonylethyl, ethylaminocarbonylmethyl, methylaminocarbonylpropyl and propylaminocarbonylmethyl. . Examples of "-(1-4C)alkylCONHdi[(1-4C)alkyl]" include dimethylaminocarbonylmethyl, (methyl)(ethyl)aminocarbonylmethyl, diethylaminocarbonylmethyl, dimethylaminocarbonylethyl, di-isopropylaminocarbonylmethyl and dimethylaminocarbonylpropyl.

Examples of "cyano((1-4C))alkyl" are cyanomethyl, cyanoethyl and cyanopropyl. Examples of "(5-7C)cycloalkyl" are cyclopentyl, cyclohexyl and cycloheptyl. Examples of "(3-8C)cycloalkyl" and "(3-7C)cycloalkyl" include "(5-7C)cycloalkyl", cyclopropyl, cyclobutyl and cyclooctyl. Examples of "(3-6C)cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. Examples of "(3-6C)cycloalkyl(1-4C)alkyl" include cyclopropylmethyl, cyclopropylethyl, cyclopropylpropyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

The term "amino(1-4C)alkyl" includes aminomethyl, aminoethyl, aminopropyl, aminoisopropyl and aminobutyl. The term "aminoethyl" includes 1-aminoethyl and 2-aminoethyl. The term "aminopropyl" includes 1-aminopropyl, 2-aminopropyl and 3-aminopropyl and an analogous convention applies to terms such as aminoethyl and aminobutyl.

Examples of "(1-4C)alkoxy(1-4C)alkoxy" are methoxymethoxy, ethoxymethoxy, ethoxyethoxy and methoxyethoxy. Examples of "hydroxy(1-4C)alkoxy" are hydroxyethoxy and hydroxypropoxy. Examples of "hydroxypropoxy" are 2-hydroxypropoxy and 3-hydroxypropoxy. Examples of "(1-4C)alkoxy(1-4C)alkyl" include methoxymethyl, ethoxymethyl, methoxyethyl, ethoxypropyl and propoxymethyl. Examples of "(1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl" include methoxymethoxymethyl, ethoxyethoxyethyl, ethoxymethoxymethyl, methoxyethoxymethyl, methoxymethoxyethyl, methoxyethoxyethyl and ethoxymethoxymethyl. Examples of "hydroxy(1-4C)alkoxy(1-4C)alkyl" are

(hydroxyethoxy)ethyl, 1-hydroxy-2-methoxyethyl, 1-methoxy-2-hydroxyethyl and (hydroxypropoxy)methyl. Examples of "di[(1-4C)alkoxy](2-4C)alkyl" include 1,2-dimethoxyethyl, 2,3,dimethoxypropyl and 1-methoxy-2-ethoxy-ethyl.

Examples of "-$S(O)_b$(1-4C)alkyl (wherein b is 0,1 or 2)" include methylthio, ethylthio, propylthio, methylsulphinyl, ethylsulphinyl, propanesulphinyl, mesyl, ethylsulphonyl, propylsulphonyl and isopropylsulphonyl. Examples of "-$OS(O)_2$(1-4C)alkyl" include methylsulfonyloxy, ethylsulfonyloxy, propylsulfonyloxy, isopropylsulfonyloxy and tert-butylsulfonyloxy. Examples of "-(1-4C)alkyl$S(O)_b$(1-4C)alkyl (wherein b is 0, 1or 2)" include methylthiomethyl, ethylthiomethyl, methylthioethyl, methylsulphinylmethyl, ethylsulphinylmethyl, propylsulphinylmethyl, mesylmethyl, ethylsulphonylmethyl, propylsulphonylmethyl and isopropylsulphonylmethyl.

Examples of "hydroxy(1-4C)alkylSO_2(1-4C)alkyl-" include hydroxymethylsulfonylmethyl, hydroxyethylsulfonylmethyl, hydroxyethylsulfonylethyl, and hydroxypropylsulfonlymethyl. Examples of "(1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-" include methoxymethylsulfonylmethyl, ethoxyethylsulfonylmethyl, methoxyethylsulfonylethyl, and methoxypropylsulfonlymethyl.

Examples of "(1-6C)alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl.

Within this specification composite terms are used to describe groups comprising more that one functionality such as –(1-4C)alkylSO_2(1-4C)alkyl. Such terms are to be interpreted in accordance with the meaning which is understood by a person skilled in the art for each component part. For example –(1-4C)alkylSO_2(1-4C)alkyl includes –methylsulphonylmethyl, -methylsulphonylethyl, -ethylsulphonylmethyl, and -propylsulphonylbutyl.

Where optional substituents are chosen from "0, 1, 2 or 3" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups. An analogous convention applies to substituents chose from "0, 1 or 2" groups, "0 or 1" group and "1 or 2" groups.

Preferred values of A, B, R^1 to R^7, m and n are as follows. Such values may be used where appropriate with any of the definitions, claims, aspects or embodiments defined hereinbefore or hereinafter.

In one embodiment of the invention are provided compounds of formula (1), in an alternative embodiment are provided pharmaceutically-acceptable salts of compounds of formula (1), in a further alternative embodiment are provided in-vivo hydrolysable esters of compounds of formula (1), and in a further alternative embodiment are provided pharmaceutically-acceptable salts of in-vivo hydrolysable esters of compounds of formula (1). In a further alternative embodiment are provided pro-drugs of compounds of formula (1) and in a still further alternative embodiment are provided pharmaceutically-acceptable salts of pro-drugs of compounds of formula (1).

In one aspect of the invention B is of the formula (2a). In another aspect of the invention B is of the formula (2b).

In one aspect of the present invention there is provided a compound of formula (1) as depicted above wherein R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$.

In another aspect of the invention R^4 and R^5 are together $-C(R^7)=C(R^6)-S-$.

In a further aspect of the invention, R^6 and R^7 are independently selected from hydrogen, halo or (1-6C)alkyl.

Preferably R^6 and R^7 are independently selected from hydrogen, chloro, bromo or methyl.

Particularly R^6 and R^7 are independently selected from hydrogen or chloro.

More particularly one of R^6 and R^7 is chloro.

In one embodiment, one of R^6 and R^7 is chloro and the other is hydrogen.

In another embodiment, both R^6 and R^7 are chloro.

In one aspect of the present invention m is 1 or 2.

In another aspect of the invention m is 1.

In another aspect of the invention, m is 0.

In one aspect of the present invention R^3 is selected from halo, cyano, hydroxy, fluoromethyl, difluoromethyl and trifluoromethyl.

In another aspect of the invention R^3 is halo.

In another aspect of the invention R^4 is selected from chloro and bromo.

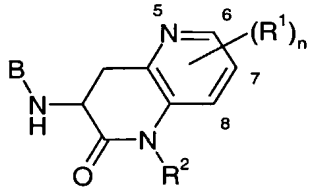
In one aspect of the present invention R^4 is selected from halo and methyl.

In another aspect of the invention R^4 is selected from methyl, chloro and fluoro.

In another aspect of the invention R^4 is selected from chloro and fluoro.

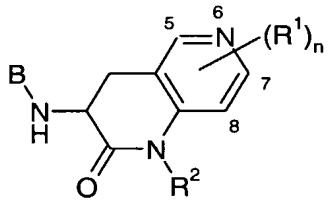
More preferably R^3 is chloro.

In one aspect of the invention the compound of formula (1) is a compound of the formula (1a):



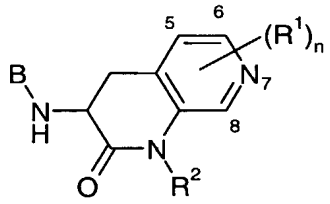
(1a)

In another aspect of the invention the compound of formula (1) is a compound of the formula (1b)



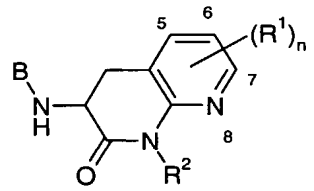
(1b)

In another aspect of the invention the compound of formula (1) is a compound of the formula (1c):



(1c)

In another aspect of the invention the compound of formula (1) is a compound of the formula (1d):



(1d)

In one aspect of the invention n is 0 or 1.

In one aspect preferably n is 1.

In another aspect, preferably n is 0.

When R^1 is a substituent at the 5-position of the pyridylene ring comprising A as hereinbefore described, R^1 is suitably selected from halo, nitro, cyano, hydroxy, carboxy,

-$S(O)_b$(1-4C)alkyl (wherein b is 0, 1, or 2), -$OS(O)_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl and trifluoromethoxy.

When R^1 is a substituent at the 5-position of the pyridylene ring comprising A as hereinbefore described, R^1 is suitably selected from halo, nitro, cyano, hydroxy, carboxy, -$S(O)_b$(1-4C)alkyl (wherein b is 0, 1, or 2), -$OS(O)_2$(1-4C)alkyl, (1-4C)alkyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy and hydroxy(1-4C)alkyl.

When R^1 is a substituent at the 5-position of the pyridylene ring comprising A as hereinbefore described, R^1 is suitably selected from halo, hydroxy, carboxy, -$S(O)_2$Me, -$OS(O)_2$Me, methyl, ethyl, -OMe, (1-4C)alkanoyl, (1-4C)alkanoyloxy and hydroxy(1-4C)alkyl.

When R^1 is a substituent at the 5-position of the pyridylene ring comprising A as hereinbefore described, R^1 is suitably selected from fluoro, chloro, hydroxy, -$S(O)_2$Me, -$OS(O)_2$Me, methyl, ethyl and -OMe.

When R^1 is a substituent at the 6-, 7- or 8-position of the pyridylene ring comprising A as hereinbefore described, $R^1$is suitably selected from fluoro, chloro, hydroxy, methyl and methoxy.

In one aspect of the invention R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl,-(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, –(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, -(1-4C)alkylSO_2Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl.

In another aspect of the invention R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, –(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, and -(1-4C)alkylSO_2Ndi[(1-4C)alkyl}.

In another aspect of the invention R^2 is selected from (1-4C)alkyl,

hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO$_2$(1-4C)alkyl, hydroxy(1-4C)alkylSO$_2$(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO$_2$(1-4C)alkyl-.

In another aspect of the invention R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, -(1-4C)alkylSO$_2$(1-4C)alkyl, hydroxy(1-4C)alkylSO$_2$(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO$_2$(1-4C)alkyl-.

In another aspect of the invention R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO$_2$(1-4C)alkyl.

In another aspect of the invention R^2 is selected from hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO$_2$(1-4C)alkyl.

In a further aspect of the invention R^2 is selected from hydroxyethyl, hydroxypropyl, dihydroxypropyl and -EtSO$_2$Me.

In one aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2a);

n is 0, 1 or 2;

R^4 and R^5 are together –S-C(R^6)=C(R^7)- or –C(R^7)=C(R^6)-S-;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo and methyl;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(1-4C)alkyl, -(1-4C)alkylSO$_2$(1-4C)alkyl, hydroxy(1-4C)alkylSO$_2$(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO$_2$(1-4C)alkyl-, –(1-4C)alkylNHSO$_2$(1-4C)alkyl, -(1-4C)alkylSO$_2$NH(1-4C)alkyl, -(1-4C)alkylSO$_2$Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2a);

n is 0, 1 or 2;

R^4 and R^5 are together –S-C(R^6)=C(R^7)- or –C(R^7)=C(R^6)-S-;

R^6 and R^7 are independently selected from hydrogen, chloro, bromo and methyl;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(1-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2a);

n is 0 or 1;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2a);

n is 0;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

R^2 is selected from 1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2a);

n is 0;

R^4 and R^5 are together $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen and chloro;

R^2 is selected from hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein B is of formula (2b);

n is 0, 1 or 2;

m is 0, 1 or 2;

R^3 is halo;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(1-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, –(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, -(1-4C)alkylSO_2Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein B is of formula (2b);

n is 0, 1 or 2;

m is 0, 1 or 2;

R^3 is halo;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(1-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein B is of formula (2b);

n is 0 or 1;

m is 0, 1 or 2;

R^3 is chloro;

R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2b);

n is 0;

m is 0, 1 or 2;

R^3 is chloro;

R^2 is selected from 1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2b);

n is 0;

m is 1;

R^3 is chloro;

R^2 is selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

In another aspect of the invention is provided a compound of the formula (I) wherein

B is of formula (2b);

n is 0;

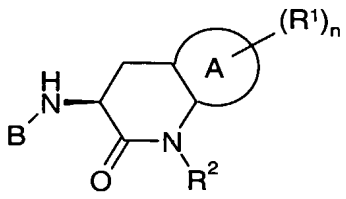
m is 1;

R^3 is chloro;

R^2 is selected from hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof.

Preferred compounds of the invention are of the formula (1e), wherein R^1 to R^7 m and n are as defined in any aspect or embodiment described hereinbefore or hereinafter.

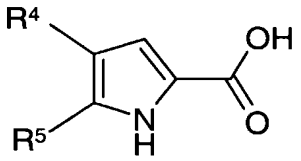


(1e)

Particular compounds of the invention are each of the Examples or a pharmaceutically acceptable salt or pro-drug thereof, each of which provides a further independent aspect of the invention. In a further aspect of the invention there is provided any two or more of the Examples or a pharmaceutically acceptable salt or pro-drug thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (1) or a pharmaceutically acceptable salt or an in-vivo hydrolysable ester thereof which process (wherein A, R^1 to R^7, m and n are, unless otherwise specified, as defined in formula (1)) comprises of:

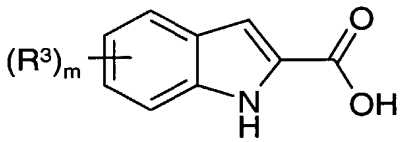
a) reacting an acid of the formula (3a)



(3a)

or an activated derivative thereof;

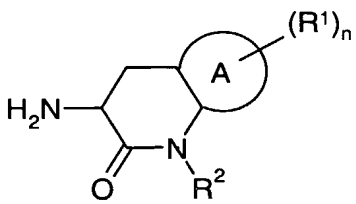
or an acid of the formula (3b)



(3b)

or an activated derivative thereof;

with an amine of formula (4):



(4)

and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

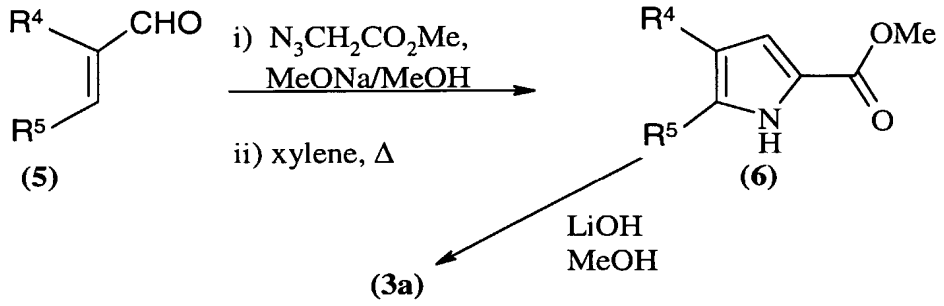
iii) forming a pharmaceutically acceptable salt and/or in-vivo hydrolysable ester.

Specific reaction conditions for the above reaction are as follows.

Process a) Acids of formula (3a) or (3b) and amines of formula (4) may be coupled together in the presence of a suitable coupling reagent. Standard peptide coupling reagents known in the art can be employed as suitable coupling reagents, or for example carbonyldiimidazole, 1-ethyl-3-(3-dimethylaminopropyl)carbodi-imide hydrochloride (EDCI) and dicyclohexyl-carbodiimide (DCCI), optionally in the presence of a catalyst such as 1-hydroxybenzotriazole, dimethylaminopyridine or 4-pyrrolidinopyridine, optionally in the presence of a base for example triethylamine, di-isopropylethylamine, pyridine, or 2,6-di-*alkyl*-pyridines such as 2,6-lutidine or 2,6-di-*tert*-butylpyridine. Suitable solvents include dimethylacetamide, dichloromethane, benzene, tetrahydrofuran and dimethylformamide. The coupling reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

Suitable activated acid derivatives include acid halides, for example acid chlorides, and active esters, for example pentafluorophenyl esters. The reaction of these types of compounds with amines is well known in the art, for example they may be reacted in the presence of a base, such as those described above, and in a suitable solvent, such as those described above. The reaction may conveniently be performed at a temperature in the range of -40 to 40°C.

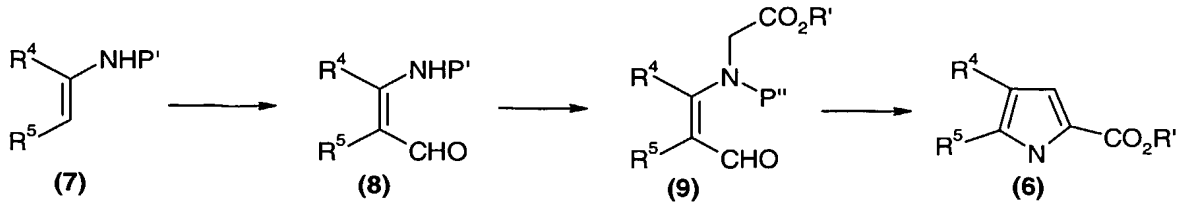
A compound of formula (3a) may be prepared according to Scheme 1:



Scheme 1

Compounds of formula (5) are commercially available or they are known compounds or they are prepared by processes known in the art.

Compounds of formula (6) may also be prepared as illustrated in Scheme 2:

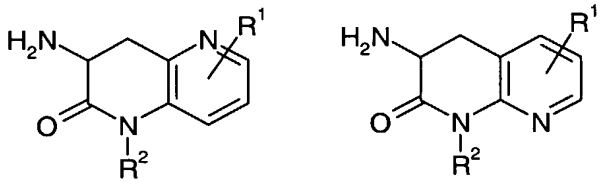


Scheme 2

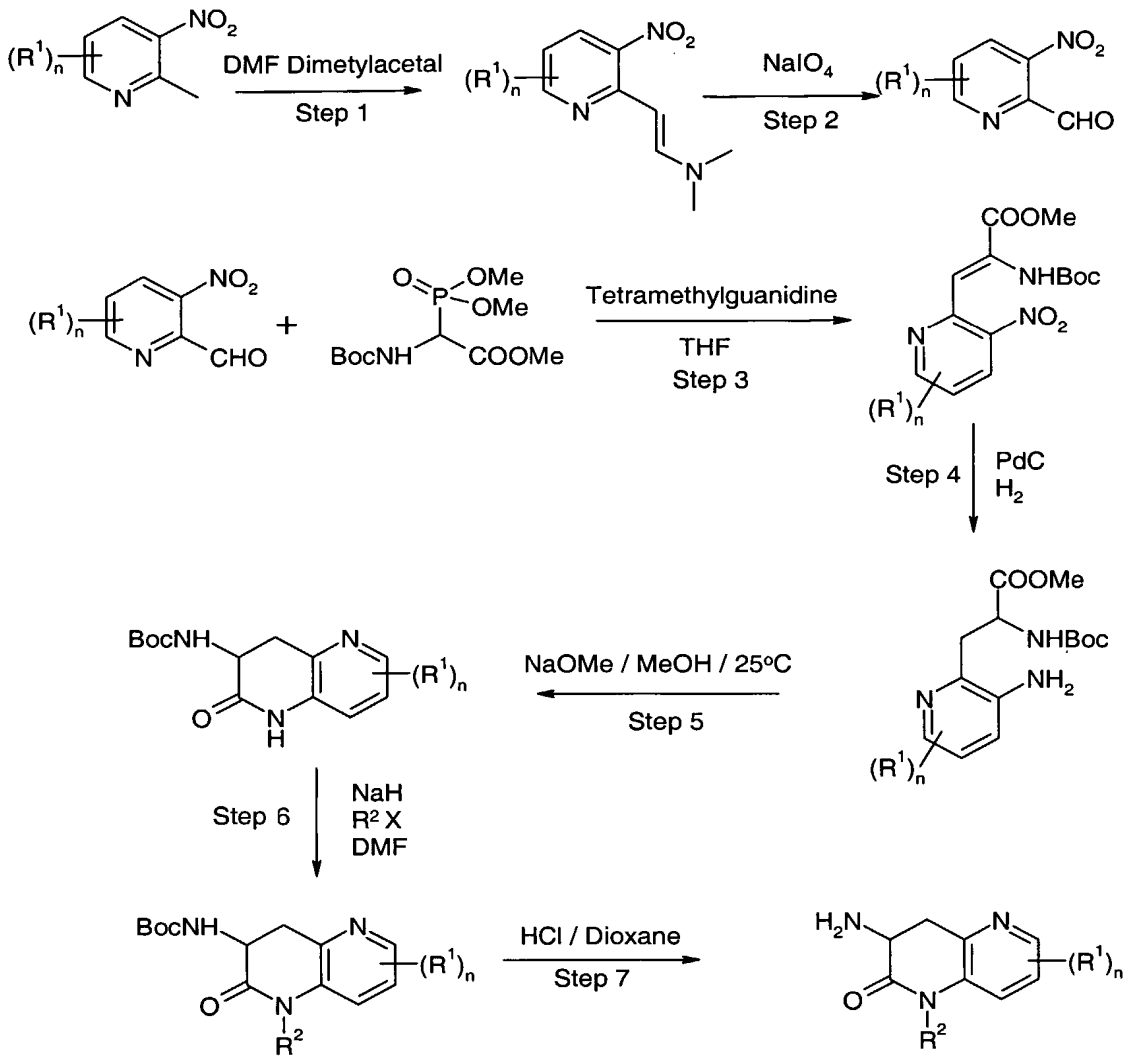
The conversion of compounds of formula (7) into compounds of formula (8) may be carried out by directed ortho lithiation reactions (J. Org. Chem, 2001, volume 66, 3662-3670), for example with n-butyl lithium and $(CHO)N(alkyl)_2$. The protecting group P' in compounds of formula (7) must be suitable directing group for this reaction and may be for example – CO_2tBu. Reaction of compounds of formula (8) with LCH_2CO_2R where L is a leaving group, and replacement of the protecting group P' with an alternative P'' (for example –COalkyl) according to standard processes, gives a compound of formula (9). This may be cyclised using a base, for example potassium carbonate or sodium methoxide.

Compounds of the formula (3b) commercially available or they are known compounds or they are prepared by processes known in the art.

Compounds of the formula (4) can be prepared from cyclisation of suitably functionalised heterocycles. For example,



compounds of formula (4a) and (4b) may be prepared from an appropriately substituted nitro-methyl pyridine or amino-pyridine according to the Schemes 3 and 4:-



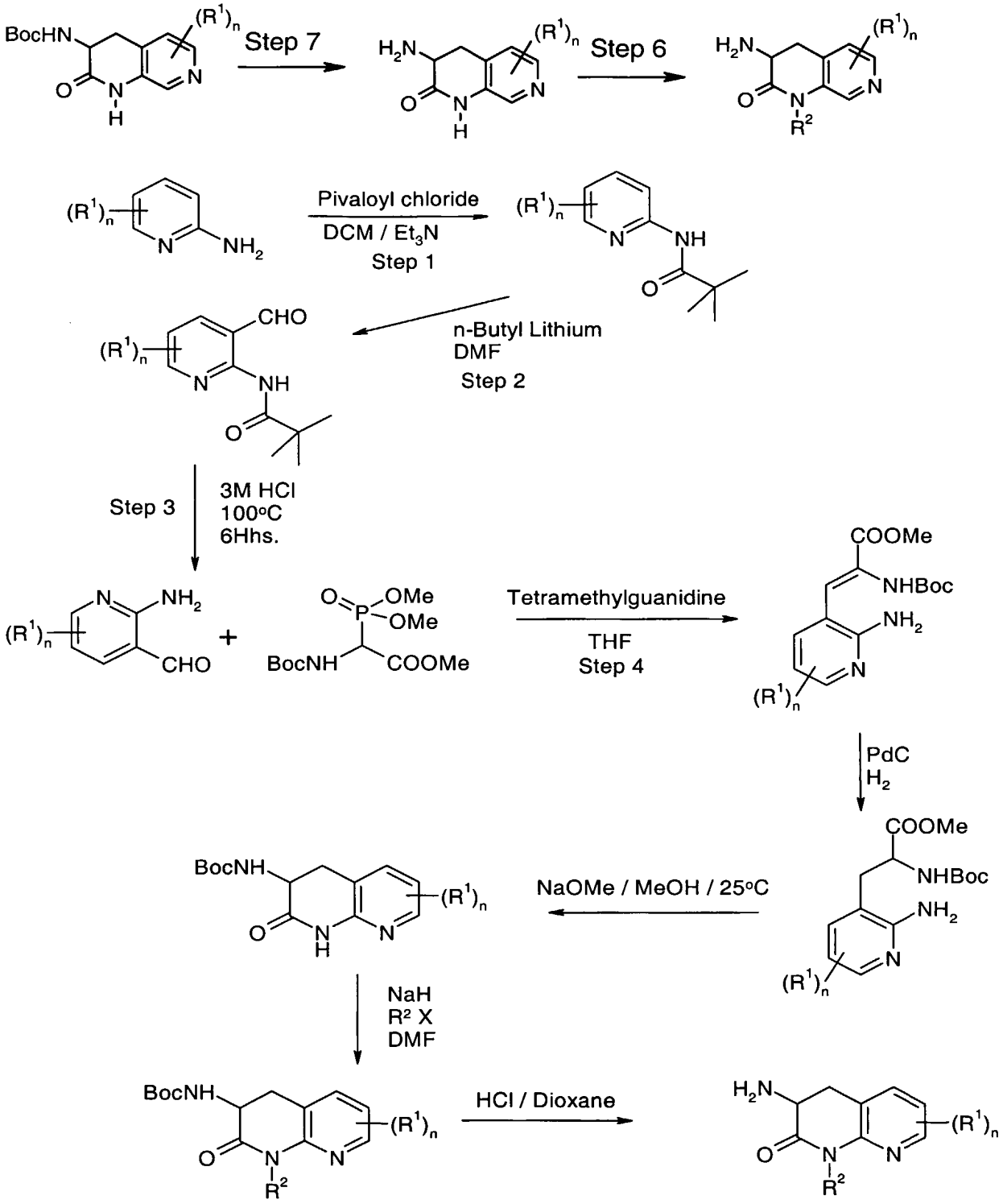
Scheme 3

Steps 1 and 2 may be carried out by the process described in Tetrahedron 1998, 54(23), 6311-6318. Step 3 may be carried out by the method described in Synthesis 1992 (5), 487.

Asymmetric hydrogenation reactions of olefins as shown in Step 4 are well known (see for example, JACS 1993, 115, 10125-10138) and lead to homochiral final products. Step 5 may alternatively be carried out by hydrolysing the ester and activating the resulting acid with a carbodiimide such as EDCI or DCCI, or by preparing an acid chloride, or activated ester such as an N –hydroxysuccinimide ester. Suitable bases are organic base such as triethylamine or di-isopropylethylamine (DIPEA) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

In Step 6, X is a leaving group, for example Cl, Br, I , -OSO_2Me (-OMesyl). In Step 7, alternative solvents such as dichloromethane or other acids such as trifluoroacetic acid can be used.

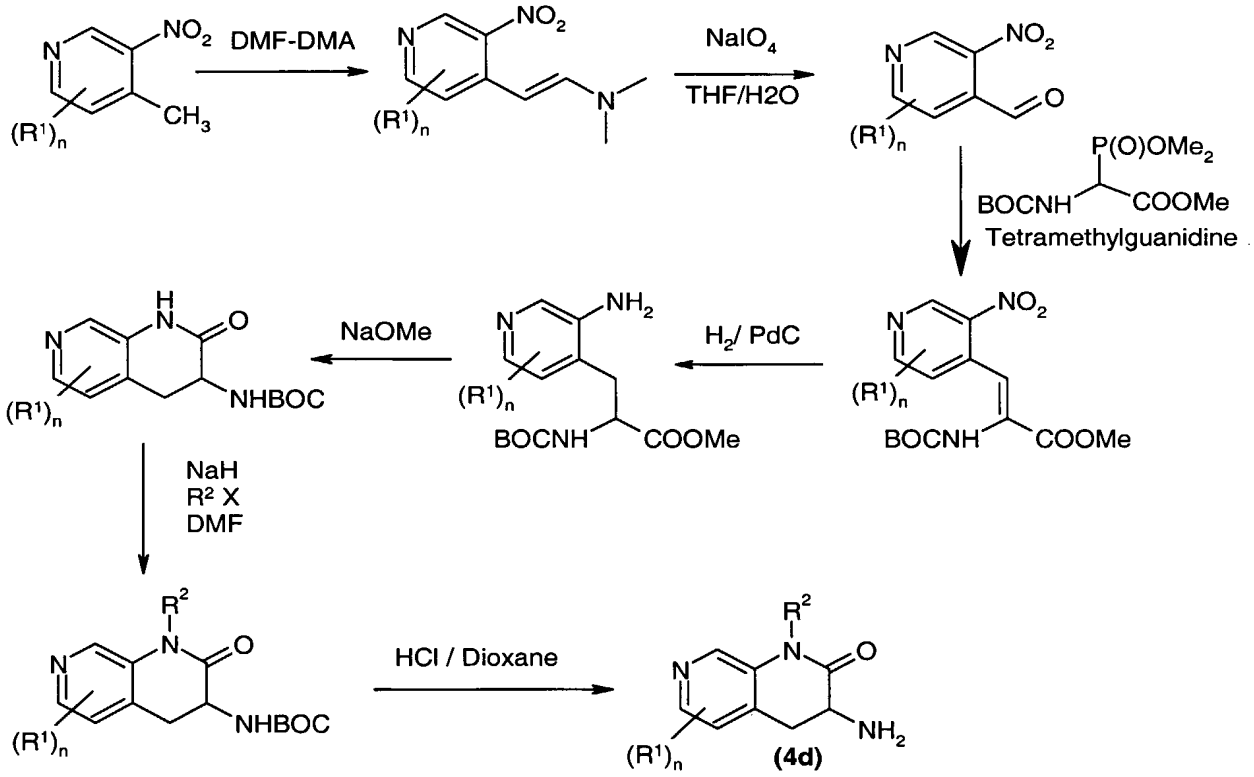
Alternatively, Step 7 may be carried out before Step 6, for example:



Scheme 4

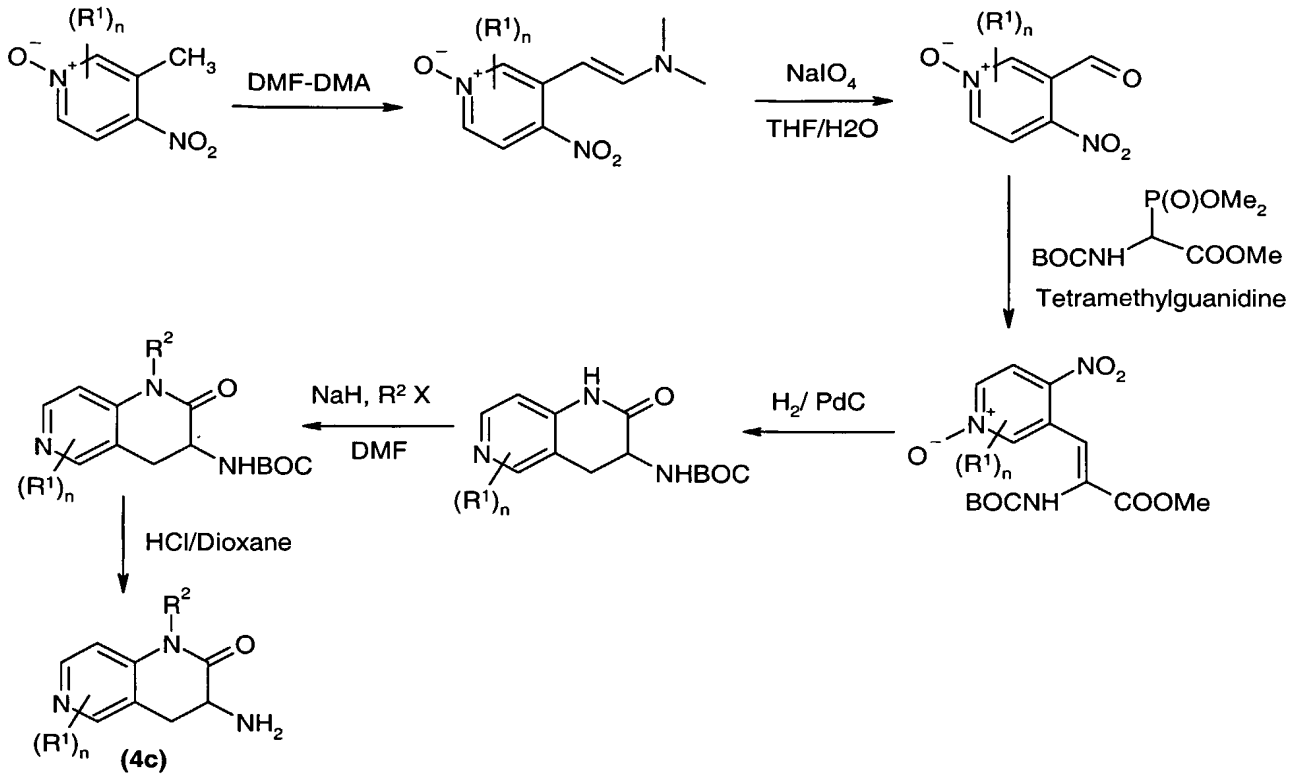
Steps 1, 2, 3 and 4 are described in JOC 1983, 48, 3401-3408.

The processes described above and shown in Schemes 3 and 4 may also be applied to other isomeric pyridines (4c) and (4d). The processes described above and shown in Schemes 3 and 4 may also be applied to other isomeric pyridines (4c) and (4d) as shown in the schemes below. Compound (4d) (**Scheme 5**) can be prepared in a similar manner to (4a) (**Scheme 3**).



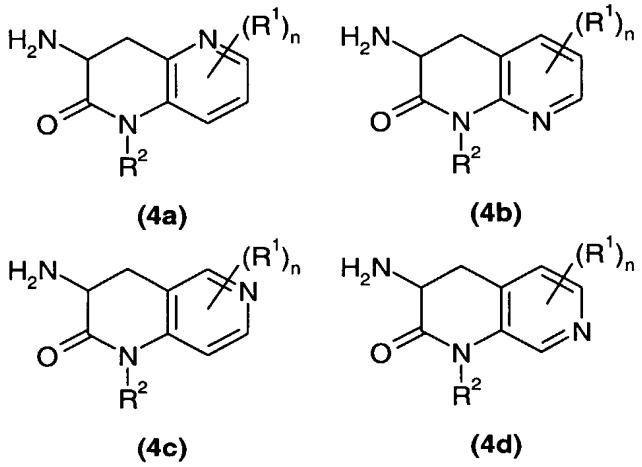
Scheme 5

Compound (4c) can be prepared in a similar manner to (4a) and (4d), starting from the known pyridine *N*-oxide (CAS Reg. No: 1074-98-2) as shown in **Scheme 6**.



Scheme 6

Certain compounds of the formula (4) are novel and each provide a further independent aspect of the invention.



Therefore in a further aspect of the invention there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0 or 1; either R^1 is a substituent at the 5-position of the pyridyl ring and is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N*,*N*-((1-4C)alkyl)$_2$carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N*,*N*-((1-4C)alkyl)$_2$sulphamoyl, -S(O)$_b$(1-4C)alkyl (wherein b is 0,1,or 2), -OS(O)$_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-

4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and $-NHSO_2$(1-4C)alkyl;

or R^1 is a substituent at the 6-, 7- or 8-position of the pyridyl ring and is independently selected from halo, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, $-$(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, -(1-4C)alkylSO_2Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl;

provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then $n \neq 0$.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0 or 1; R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy; and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then $n \neq 0$.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) and (4d), wherein n is 0 or 1; R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy; and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-;

provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then $n \neq 0$.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0 or 1, R^1 is selected from fluoro, chloro, hydroxy, methyl and

methoxy and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl;

provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then $n \neq 0$.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0 and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl; provided that, in a compound of formula (4a) or (4d) R^2 is not hydrogen.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0 and R^2 is selected from hydrogen, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl; provided that, in a compound of formula (4a) or (4d) R^2 is not hydrogen.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein n is 0.

In a further aspect of the invention, there is provided a compound of the formula (4a), (4b), (4c) or (4d), wherein R^2 is hydrogen.

A preferred compound is of formula (4b) wherein n is 0 and R^2 is hydrogen, that is the compound 3-amino-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one.

A further preferred compound is of formula (4c) wherein n is 0 and R^2 is hydrogen, that is the compound 3-amino-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one.

It will be appreciated that R^2 may be introduced before the compound of formula (3a) or (3b) is coupled with the compound of formula (4), or maybe introduced after the coupling (for example replacing a suitable protecting group). It will be appreciated that modification or replacement of the group R^2 may result in interconversion of one compound of the formula (1) into another compound of the formula (1).

It will be appreciated that certain of the various ring substituents in the compounds of the present invention, for example R^1 may be introduced by standard aromatic substitution reactions or generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions may convert one compound of the formula (1) into another compound of the formula (1). Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents

and reaction conditions for such procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; and the introduction of a halogen group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

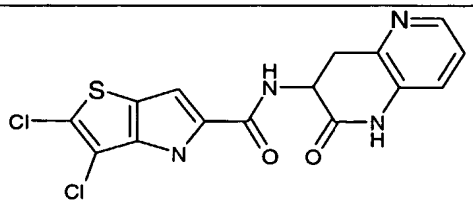
A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

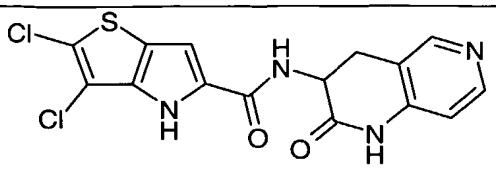
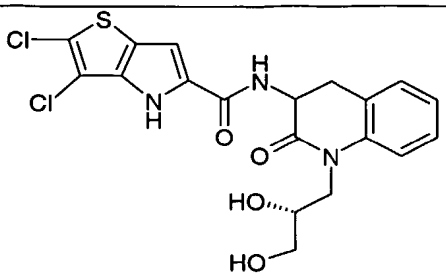
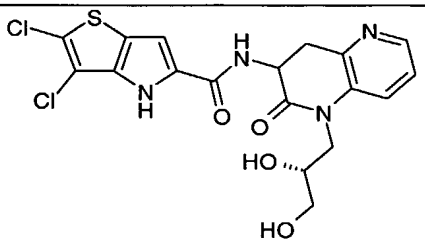
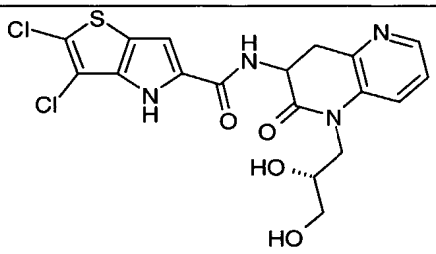
The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

Certain intermediates in the preparation of a compound of the formula (1) are novel and form another aspect of the invention.

Compounds of the invention generally possess improved physical properties (for example solubility and/or plasma-protein binding) in comparison with those of the compounds previously disclosed, for example compared with compounds not substituted on the amide nitrogen as hereinbefore discussed. In combination with glycogen phosphorylase inhibitory activity, such physical properties render the compounds of the invention particularly useful as pharmaceuticals.

The thermodynamic solubilities of Examples 8 and 9 and Reference Examples 1, 4 and 5 are given in the table below.

Example No	Structure	Solubility (μM)	Activity (μM)
Ref Example 1		1.18	0.10

Ref Example 4		1.22	0.49
Ref Example 5		3.05	0.01
Example 8*		16.2	0.06
Example 9*		179	0.168

* absolute stereochemistry of each isomer not known

The thermodynamic solubility data for the compounds of the invention as given above may be measured by agitating the compound in 0.1 M phosphate at pH7.4 for 24hours, then analysis of the supernatant (for example by LCUV/MS) using a solution (for example in DMSO) of known concentration as the calibrant.

Plasma Protein binding may be measured using an equilibrium dialysis technique, whereby compound is added to 10% plasma giving a concentration of 20 μM and dialysed with isotonic buffer for 18 hours at 37°C. The plasma and buffer solutions are analysed using LCUVMS and the first apparent binding constant for the compound derived. The binding constant is then used to determine the % free in 100% plasma.

The binding constant derived from the dialysis experiment is based upon a model of 1:1 binding between compound and albumin.

$$P + D \rightleftharpoons PD$$

$$K1 = \frac{[PD]}{[P] \times [D]}$$

where P = free protein, D = free drug, PD = drug protein complex, K1 = first apparent binding constant.

As stated hereinbefore the compounds defined in the present invention possesses glycogen phosphorylase inhibitory activity. This property may be assessed, for example, using the procedure set out below.

Assay

The activity of the compounds is determined by measuring the inhibitory effect of the compounds on glycogen degradation, the production of glucose-1-phosphate from glycogen is monitored by the multienzyme coupled assay, as described in EP 0 846 464 A2, general method of Pesce et al (Pesce, M A, Bodourian, S H, Harris, R C, and Nicholson, J F (1977) Clinical Chemistry 23, 1171 - 1717). The reactions were in 384well microplate format in a volume of 50µl. The change in fluorescence due to the conversion of the co-factor NAD to NADH is measured at 340nM excitation, 465nm emission in a Tecan Ultra Multifunctional Microplate Reader. The reaction is in 50mM HEPES, 3.5mM KH_2PO_4, 2.5mM $MgCl_2$, 2.5mM ethylene glycol-bis(b-aminoethyl ether) *N,N,N',N'*-tetraacetic acid, 100mM KCl, 8mM D-(+)-glucose pH7.2, containing 0.5mM dithiothreitol, the assay buffer solution. Human recombinant liver glycogen phosphorylase *a* (hrl GP*a*) 20nM is pre-incubated in assay buffer solution with 6.25mM NAD, 1.25mg type III glycogen at 1.25 mg ml^{-1} the reagent buffer, for 30 minutes. The coupling enzymes, phosphoglucomutase and glucose-6-phosphate dehydrogenase (Sigma) are prepared in reagent buffer, final concentration 0.25Units per well. 20µl of the hrl GPa solution is added to 10µl compound solution and the reaction started with the addition of 20ul coupling enzyme solution. Compounds to be tested are prepared in 10µl 5% DMSO in assay buffer solution, with final concentration of 1% DMSO in the assay. The non-inhibited activity of GP*a* is measured in the presence of 10µl 5% DMSO in assay buffer solution and maximum inhibition measured in the presence of 5mgs ml^{-1} N-ethylmaleimide. After 6 hours at 30°C Relative Fluoresence Units (RFUs) are measured at 340nM excitation, 465nm emission .

The assay is performed at a test concentration of inhibitor of 10μM or 100μM. Compounds demonstrating significant inhibition at one or both of these concentrations may be further evaluated using a range of test concentrations of inhibitor to determine an IC_{50}, a concentration predicted to inhibit the enzyme reaction by 50%.

Activity is calculated as follows:-

% inhibition = (1 - (compound RFUs - fully inhibited RFUs)/ (non-inhibited rate RFUs - fully inhibited RFUs)) * 100.

Typical IC_{50} values for compounds of the invention when tested in the above assay are in the range 100μM to 1nM. The preferred compounds of the invention when tested in the above assay are in the range 10μM to 1nM, more preferably 1μM to 1nM. Compounds of the Examples typically have IC_{50} values of less than 5μM and generally less than 1μM. For example, Example 15 gave an value of 0.12μM.

The inhibitory activity of compounds was further tested in rat primary hepatocytes. Rat hepatocytes were isolated by the collagenase perfusion technique, general method of Seglen (P.O. Seglen, Methods Cell Biology (1976) 13 29-83). Cells were cultured on Nunclon six well culture plates in DMEM (Dulbeco's Modified Eagle's Medium) with high level of glucose containing 10% foetal calf serum, NEAA (non essential amino acids), Glutamine, penicillin /streptomycin ((100units/100ug)/ml) for 4 to 6 hours. The hepatocytes were then cultured in the DMEM solution without foetal calf serum and with 10nM insulin and 10nM dexamethasone. Experiments were initiated after 18-20 hours culture by washing the cells and adding Krebs-Henseleit bicarbonate buffer containing 2.5mM $CaCl_2$ and 1% gelatin. The test compound was added and 5 minutes later the cells were challenged with 25nM glucagon. The Krebs-Henseleit solution was removed after 60 min incubation at 37°C , 95%O_2/5%CO_2 and the glucose concentration of the Krebs-Henseleit solution measured.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The compositions of the invention may be in a form suitable for oral use (for example as tablets, lozenges, hard or soft capsules, aqueous or oily suspensions, emulsions, dispersible powders or granules, syrups or elixirs), for topical use (for example as creams, ointments, gels, or aqueous or oily solutions or suspensions), for administration by inhalation (for example as a finely divided powder or a liquid aerosol), for administration by insufflation (for

example as a finely divided powder) or for parenteral administration (for example as a sterile aqueous or oily solution for intravenous, subcutaneous, intramuscular or intramuscular dosing or as a suppository for rectal dosing).

The compositions of the invention may be obtained by conventional procedures using conventional pharmaceutical excipients, well known in the art. Thus, compositions intended for oral use may contain, for example, one or more colouring, sweetening, flavouring and/or preservative agents. In one aspect, the compositions of the invention are in a form suitable for oral dosage.

Suitable pharmaceutically acceptable excipients for a tablet formulation include, for example, inert diluents such as lactose, sodium carbonate, calcium phosphate or calcium carbonate, granulating and disintegrating agents such as corn starch or algenic acid; binding agents such as starch; lubricating agents such as magnesium stearate, stearic acid or talc; preservative agents such as ethyl or propyl p-hydroxybenzoate, and anti-oxidants, such as ascorbic acid. Tablet formulations may be uncoated or coated either to modify their disintegration and the subsequent absorption of the active ingredient within the gastrointestinal tract, or to improve their stability and/or appearance, in either case, using conventional coating agents and procedures well known in the art.

Compositions for oral use may be in the form of hard gelatin capsules in which the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules in which the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions generally contain the active ingredient in finely powdered form together with one or more suspending agents, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as lecithin or condensation products of an alkylene oxide with fatty acids (for example polyoxethylene stearate), or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and

hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives (such as ethyl or propyl p-hydroxybenzoate, anti-oxidants (such as ascorbic acid), colouring agents, flavouring agents, and/or sweetening agents (such as sucrose, saccharine or aspartame).

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil (such as arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil (such as liquid paraffin). The oily suspensions may also contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set out above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water generally contain the active ingredient together with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients such as sweetening, flavouring and colouring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, or a mineral oil, such as for example liquid paraffin or a mixture of any of these. Suitable emulsifying agents may be, for example, naturally-occurring gums such as gum acacia or gum tragacanth, naturally-occurring phosphatides such as soya bean, lecithin, an esters or partial esters derived from fatty acids and hexitol anhydrides (for example sorbitan monooleate) and condensation products of the said partial esters with ethylene oxide such as polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening, flavouring and preservative agents.

Syrups and elixirs may be formulated with sweetening agents such as glycerol, propylene glycol, sorbitol, aspartame or sucrose, and may also contain a demulcent, preservative, flavouring and/or colouring agent.

The pharmaceutical compositions may also be in the form of a sterile injectable aqueous or oily suspension, which may be formulated according to known procedures using one or more of the appropriate dispersing or wetting agents and suspending agents, which have been mentioned above. A sterile injectable preparation may also be a sterile injectable

solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example a solution in 1,3-butanediol.

Compositions for administration by inhalation may be in the form of a conventional pressurised aerosol arranged to dispense the active ingredient either as an aerosol containing finely divided solid or liquid droplets. Conventional aerosol propellants such as volatile fluorinated hydrocarbons or hydrocarbons may be used and the aerosol device is conveniently arranged to dispense a metered quantity of active ingredient.

For further information on formulation the reader is referred to Chapter 25.2 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The amount of active ingredient that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of active agent compounded with an appropriate and convenient amount of excipients which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient. For further information on Routes of Administration and Dosage Regimes the reader is referred to Chapter 25.3 in Volume 5 of Comprehensive Medicinal Chemistry (Corwin Hansch; Chairman of Editorial Board), Pergamon Press 1990.

The compound of formula (1) will normally be administered to a warm-blooded animal at a unit dose within the range 5-5000 mg per square meter body area of the animal, i.e. approximately 0.1-100 mg/kg, and this normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-250 mg of active ingredient. Preferably a daily dose in the range of 1-50 mg/kg is employed. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

The inhibition of glycogen phosphorylase activity described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment. Simultaneous treatment may be in a single tablet or in separate tablets. For

example, in order to prevent, delay or treat type 2 diabetes mellitus, the compounds of the present invention or their pharmaceutically acceptable salts may be administered in combination with one or more of the following agent(s):

1) Insulin and insulin analogues;
2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide), prandial glucose regulators (for example repaglinide, nateglinide) and glucokinase activators
3) Agents that improve incretin action (for example dipeptidyl peptidase IV inhibitors, GLP-1 agonists)
4) Insulin sensitising agents including PPARgamma agonists (for example pioglitazone and rosiglitazone); and agents with combined PPARalpha and gamma activity
5) Agents that modulate hepatic glucose balance (for example metformin, fructose 1, 6 bisphosphatase inhibitors, glycogen synthase kinase inhibitors, glucokinase activators)
6) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
7) Agents that prevent the reabsorption of glucose by the kidney (SGLT inhibitors)
8) Agents designed to treat the complications of prolonged hyperglycaemia (for example aldose reductase inhibitors)
9) Anti-obesity agents (for example sibutramine and orlistat);
10) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPARα agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); bile acid absorption inhibitors (IBATi) and nicotinic acid and analogues (niacin and slow release formulations);
11) Antihypertensive agents such as, β blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); Calcium antagonists (eg. nifedipine); Angiotensin receptor antagonists (eg candesartan), α antagonists and diuretic agents (eg. furosemide, benzthiazide);
12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin;
13) Agents which antagonise the actions of glucagon; and
14) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin)

and steroidal anti-inflammatory agents (eg. cortisone).

According to a further aspect of the present invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use in a method of treatment of a warm-blooded animal such as man by therapy.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament.

According to an additional aspect of the invention there is provided a compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as defined hereinbefore, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

According to this another aspect of the invention there is provided the use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as defined hereinbefore in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

According to a further feature of this aspect of the invention there is provided a method of producing a glycogen phosphorylase inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (1).

According to this further feature of this aspect of the invention there is provided a method of treating type 2 diabetes in a warm-blooded animal, such as man, in need of such

treatment which comprises administering to said animal an effective amount of a compound of formula (1).

As stated above the size of the dose required for the therapeutic or prophylactic treatment of a particular cell-proliferation disease will necessarily be varied depending on the host treated, the route of administration and the severity of the illness being treated. A unit dose in the range, for example, 1-100 mg/kg, preferably 1-50 mg/kg is envisaged.

In addition to their use in therapeutic medicine, the compounds of formula (1) and their pharmaceutically acceptable salts are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of cell cycle activity in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

Examples

The invention will now be illustrated by the following examples in which, unless stated otherwise:

(i) temperatures are given in degrees Celsius (°C); operations were carried out at room or ambient temperature, that is, at a temperature in the range of 18-25°C and under an atmosphere of an inert gas such as argon;

(ii) organic solutions were dried over anhydrous magnesium sulphate; evaporation of solvent was carried out using a rotary evaporator under reduced pressure (600-4000 Pascals; 4.5-30 mmHg) with a bath temperature of up to 60°C;

(iii) chromatography means flash chromatography on silica gel; thin layer chromatography (TLC) was carried out on silica gel plates;

(iv) in general, the course of reactions was followed by TLC and reaction times are given for illustration only;

(v) yields are given for illustration only and are not necessarily those which can be obtained by diligent process development; preparations were repeated if more material was required;

(vi) where given, NMR data is in the form of delta values for major diagnostic protons, given in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard,

determined at 300 MHz using perdeuterio dimethyl sulphoxide (DMSO-δ_6) as solvent unless otherwise indicated, other solvents (where indicated in the text) include deuterated chloroform $CDCl_3$; peak multiplicities are shown as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; q, quartet, quin, quintet;

(vii) chemical symbols have their usual meanings; SI units and symbols are used;

(viii) reduced pressures are given as absolute pressures in Pascals (Pa); elevated pressures are given as gauge pressures in bars;

(ix) solvent ratios are given in volume : volume (v/v) terms;

(x) mass spectra (MS) were run with an electron energy of 70 electron volts in the chemical ionisation (CI) mode using a direct exposure probe; where indicated ionisation was effected by electron impact (EI), fast atom bombardment (FAB) or electrospray (ESP); values for m/z are given; generally, only ions which indicate the parent mass are reported and unless otherwise stated the value quoted is $(M-H)^-$;

(xi) The following abbreviations may be used:

SM	starting material;
EtOAc	ethyl acetate;
MeOH	methanol;
EtOH	ethanol;
DCM	dichloromethane;
HOBT	1-hydroxybenzotriazole;
DIPEA	di-isopropylethylamine;
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride;
Et_2O	"ether" = diethyl ether;
THF	tetrahydrofuran;
DMF	*N*, *N*-dimethylformamide;
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluroniumhexafluorophosphate
EDAC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride
TFA	Trifluoroacetic acid
DMTMM	4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride

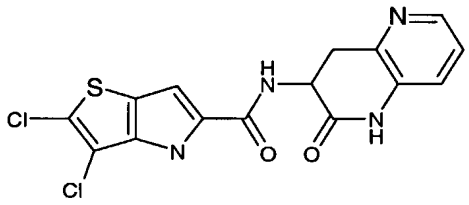
DMA N, N-dimethylacetamide

Dioxane is 1,4-dioxane

The Examples and Intermediates were named using the "Name" module in the ACD 5.0 program suite [Advanced Chemistry Development (Toronto, Canada)].

Intermediates 17, 18, 19, 20 and 21, and Reference Examples 3, 4, 6 and 7 also possess glycogen phosphorylase inhibitory activity and are each provided as a further independent aspect of the invention, together with their pharmaceutically-acceptable salts and pro-drugs.

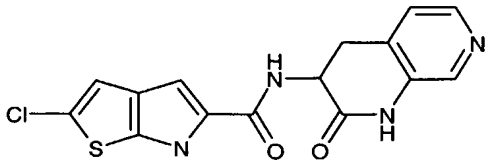
Reference Example 1: 2,3-Dichloro-*N*-(2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Triethylamine (404 mg, 4 mmol), HOBT (148.5mg, 1.1 mmol), 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14**, 234mg, 1.0 mmol) and 3-amino-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 36**, 234mg, 1.0 mmol) were dissolved in dimethylformamide (20 mL). EDCI (210mg, 1.1 mmol.) was then added and the reaction mixture stirred at ambient temperature for 2 hours. The reaction mixture was concentrated to small volume and diluted with water (50mL). The resulting precipitate was collected by filtration, washed with methanol (2 x 10mL) and ether and dried under vacuum at 50^0C to give the title compound. (237mg,71%)

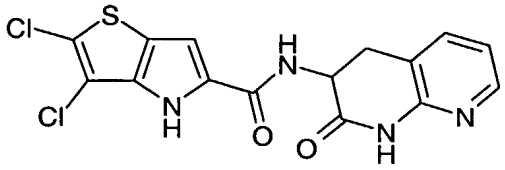
^{1}H NMR δ: 3.1-3.4 (m, 2H); 4.85 (m, 1H); 7.2 (m, 3H); 8.1 (d, 1H); 8.6 (d, 1H); 10.44 (s, 1H); 12.48 (s, 1H); MS m/z 379.

Reference Example 2: 2-Chloro-*N*-(2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



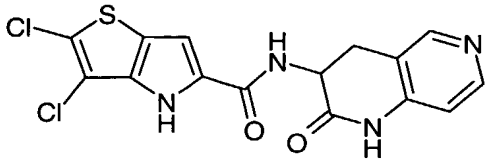
DIPEA (297 mg, 2.3mmol), HOBT (128 mg, 0.95 mmol), 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 13**, 154 mg., 0.767 mmol) and 3-amino-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one (**Intermediate 32**, 300 mg, 0.767 mmol) were suspended in DCM (10 mL). EDCI (183 mg, 0.95mmol) was then added and the reaction mixture stirred at ambient temperature for 2 hrs. The reaction mixture was filtered and the filtrate was diluted with ethyl acetate (100 mL), washed with saturated aqueous sodium bicarbonate (2 x 25mL) and brine (25mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a light brown solid which was washed with methanol (20mL) and dried to give the title compound (45mg, 17%). ^{1}H NMR δ: 3.1 (m, 2H); 4.7 (m, 1H); 7.05 (s, 1H); 7.15 (s, 1H); 7.25 (d, 1H); 8.15 (m, 2H); 8.5 (d, 1H); 10.5 (s, 1H); 11.9 (s, 1H). MS m/z 345.

Reference Example 3: 2,3-Dichloro-*N*-(2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



DIPEA (504 mg, 3.98 mmol), HOBT (134 mg., 0.995 mmol), 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 213 mg, 0.905 mmol) and 3-amino-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 22,** 212 mg, 0.905 mmol) were dissolved in DMF (10 mL). EDCI (216 mg, 1.13 mmol) was then added and the reaction mixture stirred at ambient temperature for 2 hrs. The reaction mixture diluted with water (50 mL) and the resulting precipitate was recovered by filtration, washed with methanol and dried under vacuum to give the title compound (179mg, 52%) as a cream solid. ^{1}H NMR δ: 3.1 (m, 2H); 4.8 (m, 1H); 7.0 (m, 1H); 7.2 (s, 1H); 7.6 (d, 1H); 8.15 (d, 1H); 8.6 (d, 1H); 10.7 (s, 1H); 12.5 (s, 1H). MS m/z 381.

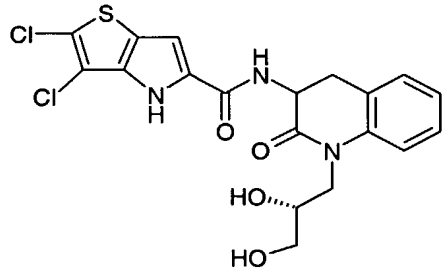
Reference Example 4: 2,3-Dichloro-*N*-(2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



DIPEA (506 mg, 4.0 mmol), HOBT (149 mg., 1.1 mmol), 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 236 mg., 1.1 mmol) and 3-amino-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 29,** 235 mg, 1.0 mmol) were dissolved in DMF (10 mL). EDCI (235 mg, 1.25 mmol.) was then added and the reaction mixture stirred at ambient temperature for 2 hrs. The reaction mixture diluted with water (50 mL) and the resulting precipitate was recovered by filtration and dried under vacuum to give the title compound (350mg, 91%) as a white solid.

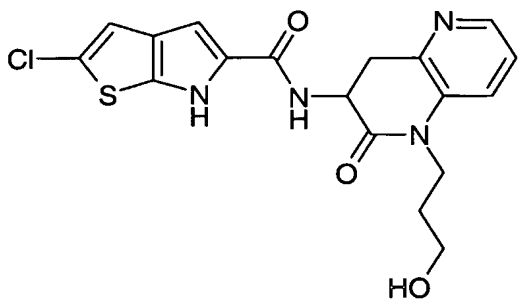
^{1}H NMR δ: 3.1 (m, 2H); 4.8 (m, 1H); 6.8 (d, 1H); 7.2 (s, 1H); 8.3 (d, 1H); 8.35 (s, 1H); 8.6 (d, 1H); 10.65 (s, 1H); 12.5 (s, 1H). MS m/z 381.

Reference Example 5: 2,3-Dichloro-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydroquinolin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



This compound is Example 40 of International Patent Application WO03/074532.

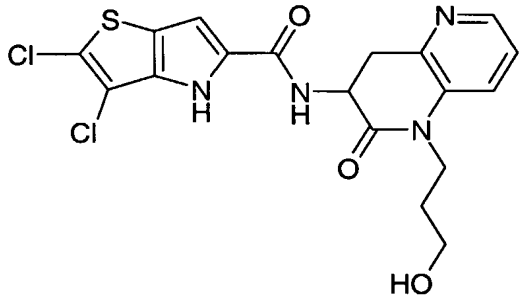
Example 1: 2-Chloro-*N*-[1-(3-hydroxypropyl)-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



2-Chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 13**, 89mg, 0.45mmol), 3-amino-1-(3-hydroxypropyl)-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 1,** 130mg, 0.45mmol), HOBT (75mg, 0.56mmol) and DIPEA (0.303mL, 1.78 mmol) were suspended in DMF (5mL) and stirred at ambient temperature. EDCI (106mg, 0.56 mmol) was added and stirring was continued for a further 6 hours. The reaction mixture diluted with ethyl acetate (50 mL) and washed with water (3 x 10mL) and brine (10mL), dried ($MgSO_4$) and evaporated to give a dark oil. The crude material was purified by flash column chromatography on silica gel eluting with a mixture of 5% methanol in DCM to give the title compound (110mg, 63%) as a pale brown solid.

^{1}H NMR δ: 1.65 (m,2H), 3.15 (m,1H), 3.3 (m,1H), 3.5 (m,2H), 3.95 (m,2H), 4.5 (b,1H), 4.9 (m,1H), 7.1 (s,1H), 7.2 (s,1H), 7.35 (m,1H), 7.6 (d,1H), 8.2(d,1H), 8.55 (d,1H), 11.95 (s,1H); MS m/z 405 (M+H).

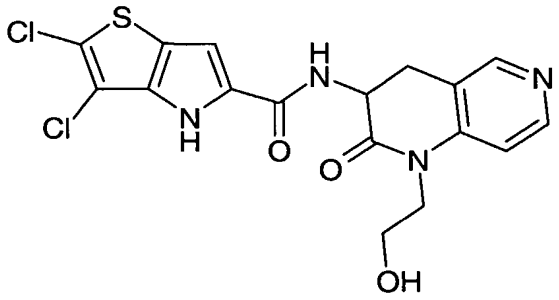
Example 2: 2,3-Dichloro-*N*-[1-(3-hydroxypropyl)-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14**, 105 mg, 0.445 mmol) and 3-amino-1-(3-hydroxypropyl)-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 1,** 130 mg, 0.45mmol) by the same process as used for **Example 1**.

^{1}H NMR δ: 1.7 (m,2H), 3.15 (m,1H), 3.3 (m,1H), 3.5 (m,2H), 3.95 (m,2H), 4.55 (t,1H), 4.9 (m,1H), 7.2 (s,1H), 7.3 (m,1H), 7.6 (d,1H), 8.2(d,1H), 8.6 (d,1H), 12.5 (s,1H); MS m/z 439, 437 (M-H).

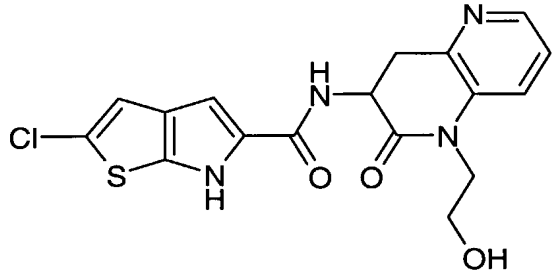
Example 3: 2,3-Dichloro-*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 95.5mg, 0.4mmol) and 3-amino-1-(2-hydroxyethyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 2**, 113mg, 0.4mmol) by the same process as used for **Example 1**.

^{1}H NMR δ: 3.1 (m,2H), 3.6 (m,2H), 3.95 (m,1H), 4.05 (m,1H), 4.85 (m,2H), 7.2 (s,1H), 7.25 (d,1H), 8.38 (s,1H), 8.4(d,1H), 8.65 (d,1H), 12.48 (s,1H); MS m/z 425 (M+H).

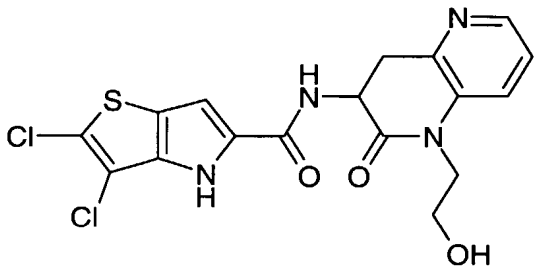
Example 4: 2-Chloro-*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl]-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Prepared from 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 13,** 286mg, 1.425 mmol) and 3-amino-1-(2-hydroxyethyl)-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 2**, 399 mg, 1.425 mmol) by the same process as used for **Example 1**.

^{1}H NMR δ: 3.1 (m,1H), 3.35 (m,1H), 3.6 (m,2H), 3.95 (m,1H), 4.0 (m,1H), 4.9 (m,2H), 7.1 (s,1H), 7.2 (s,1H), 7.3 (m,1H), 7.7 (d,1H), 8.2 (d,1H), 8.5(d,1H), 11.6 (s,1H); MS m/z 391 (M+H).

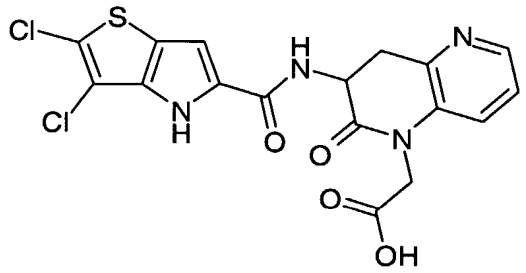
Example 5: 2,3-Dichloro-*N*-[1-(2-hydroxyethyl)-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl]-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



[3-{[(2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl]acetic acid (**Example 6,** 240 g, 0.55 mmol) was suspended in dry THF (20 mL) and cooled to 5 °C. Triethylamine (0.084ml, 0.6mmol) was added and then triethyl chloroformate (0.057 mL, 0.6mmol). The mixture was stirred at 5 °C and after 0.5 hours lithium borohydride (0.34 mL, 2.0M in THF, 0.68mmol) was added dropwise. Stirring was continued at ambient temperature for a further 16 hours. Ethyl acetate (40mL) and water (20mL) was added . The organic layer was separated, washed with water (40mL), brine (10mL), dried ($MgSO_4$) and evaporated to give a yellow solid which was purified by chromatography on silica gel, eluting with DCM containing an increasing proportion of methanol (0-10%) to give the title compound (83mg, 36%).

^{1}H NMR δ: 3.1 (m,1H), 3.35 (m,1H), 3.6 (m,2H), 3.9 (m,1H), 4.05 (m,1H), 4.9 (m,2H), 7.2 (s,1H), 7.3 (m,1H), 7.7 (d,1H), 8.2 (d,1H), 8.6 (d,1H), 12.5 (s,1H); MS m/z 425 (M+H).

Reference Example 6: [3-{[(2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl]acetic acid

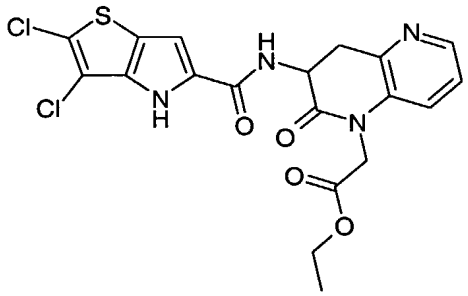


Ethyl [3-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl]acetate (**Reference Example 7**, 545mg, 1.17mmol) was dissolved in a mixture of THF (60 mL) and ethanol (20mL). Sodium hydroxide (1.17mL, 2M in water, 2.34 mmol) was added and the mixture was stirred at ambient temperature for 1 hour. The volatiles were then removed by evaporation under reduced pressure and the residue dissolved

in water (20mL). The solution was acidified with 1.0M citric acid and extracted with ethyl acetate (2 x 20mL). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$) and evaporated to give the title compound (293 mg, 57%).

^{1}H NMR δ: 3.33 (m,2H), 4.5 (d,1H), 4.7 (d,1H), 4.9 (m,1H), 7.2 (s,1H), 7.3 (m,1H), 7.45 (d,1H), 8.2 (d,1H), 8.8 (d,1H), 12.48 (s,1H); MS m/z 439 (M+H).

Reference Example 7: Ethyl [3-{[(2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrol-5-yl)carbonyl]amino}-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl]acetate

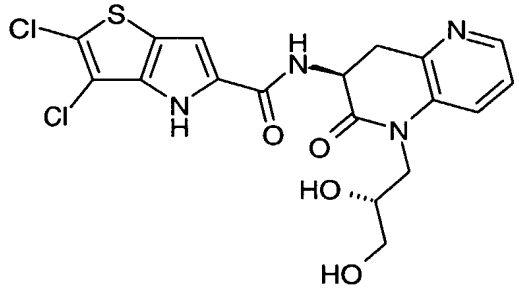


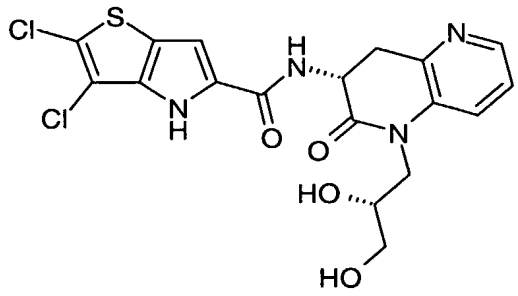
Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 479 mg, 2.0 mmol) and ethyl (3-amino-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl)acetate dihydrochloride (**Intermediate 5**, 653 mg, 2.0mmol) by a similar process to that used for **Example 1**.

^{1}H NMR δ: 1.2 (t,3H), 3.2 (m,1H), 3.4 (m,1H), 4.05 (q,2H), 4.65 (d,1H), 4.8 (d,1H), 4.9 (m,1H), 7.2 (s,1H), 7.3 (m,1H), 7.5 (d,1H), 8.2 (d,1H), 8.7(d,1H), 12.45 (s,1H); MS m/z 467 (M+H).

Example 8: 2,3-Dichloro-*N*-{(3*S*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 9: 2,3-Dichloro-*N*-{(3*R*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide





2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 719 mg, 3.05 mol), 3-amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 6,** 939 mg, 3.05 mmol), HOBT (514mg, 3.81mmol) and DIPEA (2.12 mL, 12.2mmol) were suspended in DMF (15mL) and stirred at ambient temperature. EDCI (728 mg, 3.81mmol) was added and stirring was continued for a further 4 hours. The reaction mixture diluted with water (150 mL) and the resulting precipitate recovered by filtration. The solid was then dissolved in ethyl acetate (150 mL) and washed with water (2 x 50mL) and brine (50 mL), dried (MgSO4) and evaporated to give a yellow solid which was purified by flash column chromatography on silica gel eluting with DCM containing an increasing proportion of methanol (0-10%) to give pale yellow solid, (570mg) containing a mixture of diastereomers.

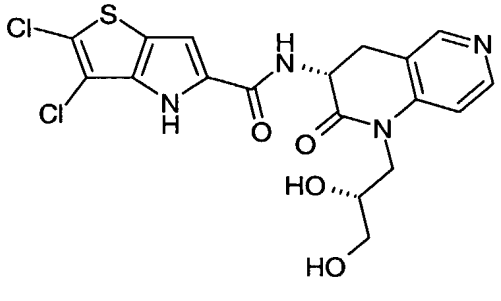
Chromatographic separation of the above mixture (242mg, 250mmx 4.6mm Chromasil CHI TBB column eluting with a mixture of isohexane/ethyl acetate/acetic acid/ triethylamine (50/50/0.1/0.05))afforded the title compounds:

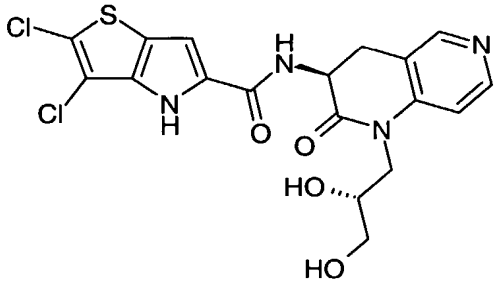
First eluting component - Isomer A (131mg, 0.29mmol): ^{1}H NMR δ: 3.2 dd,1H), 3.4 (m,3H), 3.8 (m,2H), 4.1 (m,1H), 4.7 (t,1H), 5.0 (m,2H), 7.25 (s,1H), 7.35 (m,1H), 7.8 (d,1H), 8.3 (d,1H), 8.7 (d,1H), 12.6 (bs,1H); MS m/z 455, 453 (M-H).

Second eluting component - Isomer B (81mg, 0.18mmol): ^{1}H NMR δ: 3.2 (dd,1H), 3.4 (m,3H), 3.8 (m,1H), 3.9 (m,1H), 4.1 (m,1H), 4.65 (t,1H), 4.9 (d,1H), (m,1H), 7.25 (s,1H), 7.4 (m,1H), 7.8 (d,1H), 8.3 (d,1H), 8.7 (d,1H), 12.6 (bs,1H); MS m/z 455, 453 (M-H).

Example 10: 2,3-Dichloro-*N*-{(3*S*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 11: 2,3-Dichloro-*N*-{(3*R*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide





Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 325 mg, 1.38 mmol) and 3-amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,6-

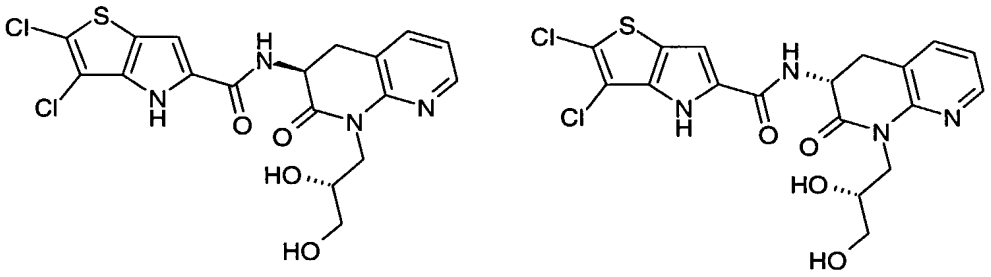
naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 7**, 425 mg, 1.38 mmol) by the same process and chromatographic separation as that used for **Examples 8 and 9.**

First eluting component: ^{1}H NMR δ: 3.15 (m,2H), 3.45 (m,2H), 3.8 (m,2H), 4.0 (m,1H), 4.65 (t,1H), 4.85 (m,1H), 4.95 (d,1H), 7.2 (s,1H), 7.3 (d,1H), 8.4 (m,2H), 8.7 (d,1H), 12.5 (s,1H); MS m/z 455, 453 (M-H).

Second eluting component: ^{1}H NMR δ: 3.15 (m,2H), 3.4 (m,2H), 3.65 (m,1H), 3.95 (m,2H), 4.65 (t,1H), 4.8 (m,2H), 7.2 (s,1H), 7.3 (d,1H), 8.4 (m,2H), 8.65 (d,1H), 12.5 (s,1H); MS m/z 455, 453 (M-H).

Example 12: 2,3-Dichloro-*N*-{(3*S*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Example 13: 2,3-Dichloro-*N*-{(3*R*)-1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

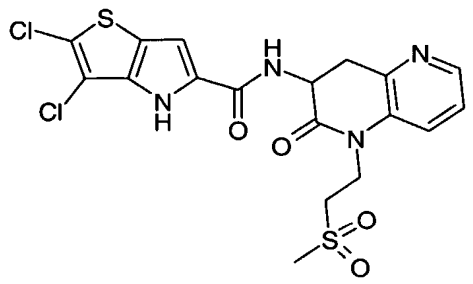


Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 471 mg, 2.0 mmol) and 3-amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one dihydrochloride ((**Intermediate 8**, 619 mg, 2.0 mmol) by the same process and chromatographic separation as that used for **Examples 8 and 9.**

First eluting component: ^{1}H NMR δ: 3.15 (m,2H), 3.3 (m,2H), 3.85 (m,1H), 4.1 (m,1H), 4.25 (m,1H), 4.5 (b,1H), 4.75 (b,1H), 4.85 (q,1H), 7.1 (m,1H), 7.2 (s,1H), 7.75 (d,1H), 8.3 (d,1H), 8.7 (d,1H), 12.5 (s,1H)

Second eluting component: ^{1}H NMR δ: 3.1 (m,2H), 3.35 (m,2H), 3.85 (m,1H), 3.95 (m,1H), 4.3 (m,1H), 4.45 (b,1H), 4.65 (b,1H), 4.85 (q,1H), 7.1 (m,1H), 7.2 (s,1H), 7.75 (d,1H), 8.35 (d,1H), 8.7 (d,1H), 12.5 (s,1H)

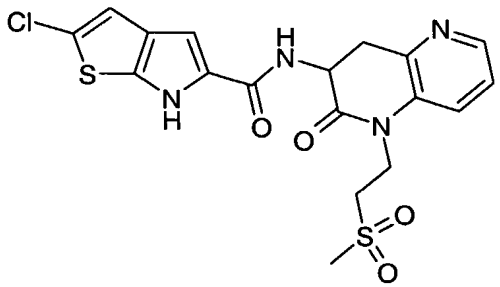
Example 14: 2,3-Dichloro-*N*-{1-[2-(methylsulfonyl)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



2,3-Dichloro-*N*-{1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Intermediate 20**; 99 mg, 0.22 mmol) was dissolved in DMF (10 mL) and cooled in an ice bath. 3-Chloroperbenzoic acid, 70% (118 mg, 0.4 mmol) was added and the mixture stirred at ambient temperature for 18 hours. Water (20mL) was added and the mixture extracted with ethyl acetate (2 x 20mLl). The combined extracts were washed with water (3 x 20mL) and saturated sodium bicarbonate (2 x 20mL), dried ($MgSO_4$) and evaporated to give a gum which was purified by chromatography on silica gel eluting with DCM containing an increasing proportion of methanol (0-10%) to give the title compound (46 mg, 43%).

^{1}H NMR δ: 3.0 (s,3H), 3.2 (t,1H), 3.2 (m,2H), 3.75 (dd,1H), 4.4 (m,1H), 4.55 (m,1H), 5.0 (m,1H), 6.85 (s,1H), 7.15 (d,1H), 7.3 (m,1H), 7.5 (d,1H), 8.4 (d,1H), 10.0 (s,1H); MS m/z 487, 485 (M-H).

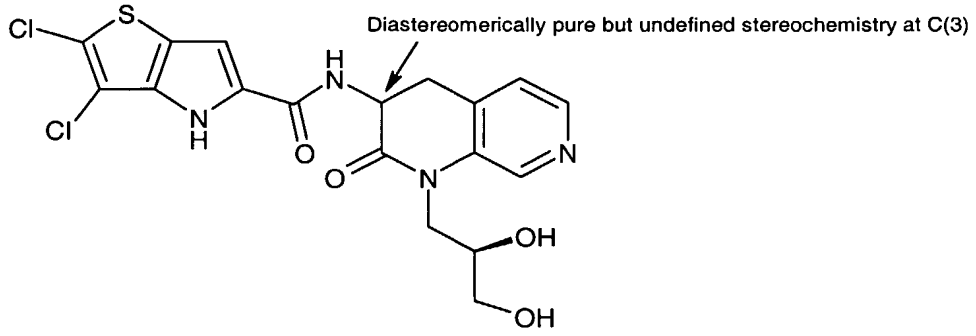
Example 15: 2-Chloro-*N*-{1-[2-(methylsulfonyl)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Prepared by the same process as **Example 14** from 2-chloro-*N*-{1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide (**Intermediate 21**).

^{1}H NMR δ: 3.0 (s,3H), 3.2 (t,1H), 3.4 (m,2H), 3.8 (dd,1H), 4.4 (m,1H), 4.5 (m,1H), 4.9 (m,1H), 6.8 (s,1H), 6.85 (s,1H), 7.0 (d,1H), 7.3 (m,1H), 7.5 (m,1H), 8.4 (d,1H), 10.24 (s,1H); MS m/z 453, 451 (M-H).

Example 18: (3*R* or *S*)-2,3-Dichloro-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

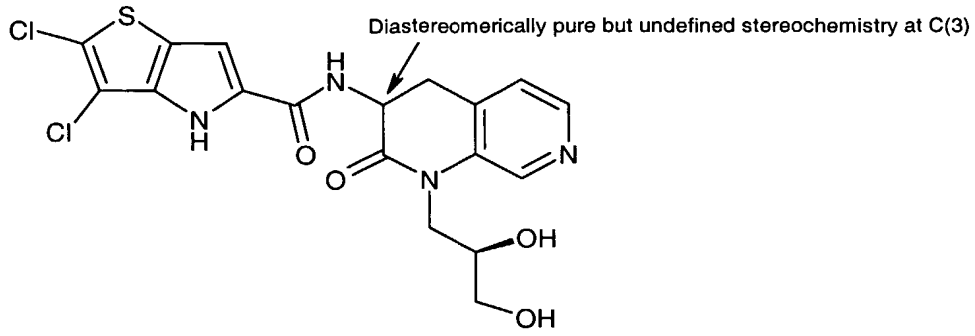


(3*R* or *S*)-2,3-Dichloro-*N*-(1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (Isomer A: **Intermediate 17**; 524 mg, 1.06 mmol) was dissolved in THF (8 mL) and HCl (4 mL, 6% aqueous) added and the reaction stirred at ambient temperature for 18 hours. The solvent was removed under reduced pressure and the pH of the solution was raised to 7 by the addition of saturated aqueous sodium bicarbonate. The resulting precipitate was filtered, washed with water (3 x 20 mL) and dried to afford the title compound (450 mg, 93%) as a solid.

^{1}H NMR δ: 3.15 (m, 2H), 3.45 (d, 2H), 3.85 (m, 2H), 4.1 (m, 1H), 4.75 (br s, 1H), 4.82 (m, 1H), 5.0 (br s, 1H), 7.2 (s, 1H), 7.3 (d, 1H), 8.23 (d, 1H), 8.62 (m, 2H), 12.5 (br s, 1H); MS m/z 455.

The alternative C(3) diastereomer was made in a similar manner to **Example 18,** starting from **Intermediate 18:**

Example 19: (3*S* or *R*)-2,3-Dichloro-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



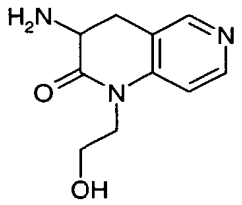
^{1}H NMR δ: 3.15 (m, 2H), 3.38 (m, 2H), 3.75 (m, 2H), 3.95 (dd, 1H), 4.1 (dd, 1H), 4.7 (br s, 1H), 4.8 (m, 2H), 7.2 (s, 1H), 7.33 (d, 1H), 8.25 (d, 1H), 8.6 (s, 1H), 8.72 (d, 1H), 12.5 (br s, 1H); MS m/z 455.

Intermediate 1: 3-Amino-1-(3-hydroxypropyl)-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride

A solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl)carbamate (**Intermediate 15,** 329 mg, 1.25 mmol) in DMF (3 mL) was added to a suspension of sodium hydride (55 mg, 60% dispersion in mineral oil, 1.38mmol) in DMF (1 mL). The mixture was stirred under nitrogen at ambient temperature for 0.5 hours. 2-(3-bromopropoxy)tetrahydro-2*H*-pyran (278 mg,1.25 mmol) was then added and stirring was continued for a further 18 hour. The reaction mixture was diluted water (20 mL) and extracted with ethyl acetate (3 x 20mL). The combined extracts were washed with water (2 x 20mL) and brine (20 mL), dried ($MgSO_4$) and evaporated to give a yellow oil. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate to give a foam. This material was dissolved in DCM (5mL), treated with 4.0M HCl in dioxane (10 mL) and stirred at ambient temperature for 2 hours. Ether (50 mL) was added and the white solid precipitate recovered by filtration and dried under vacuum to give the title compound (270mg, 73%) as a solid.

^{1}H NMR δ: (m,2H), 3.4m (m,1H), 3.6 (m,3H), 4.0 (t,2H), 4.5 (m,1H), 7.6 (m,1H), 7.9 (d,1H), 8.3 (d,1H), 8.8 (b,3H); MS m/z 222.

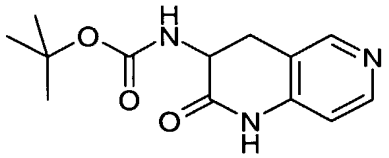
Intermediate 2: 3-Amino-1-(2-hydroxyethyl)-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one dihydrochloride



A solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)carbamate (**Intermediate 3,** 231mg, 0.88mmol) in DMF (3 mL) was added to a suspension of sodium hydride (35 mg, 60% dispersion in mineral oil, 1.38 mmol) in DMF (1 mL). The mixture was stirred under nitrogen at ambient temperature for 0.5 hours. 2-(2-Bromoethoxy)tetrahydro-2*H*-pyran (247mg, 0.96mmol) was then added and the reaction mixture heated at 90 °C for 3 hours. After cooling to ambient temperature the solution was diluted with ethyl acetate (50 mL) and washed with water (3 x 10mL) and brine (10 mL), dried ($MgSO_4$) and evaporated to give a yellow oil. The crude material was purified by flash column chromatography on silica gel eluting with ethyl acetate to give a crystalline solid. This material was dissolved in DCM (5 mL), treated with 4.0M HCl in dioxane (5mL) and stirred at ambient temperature for 2 hours. Ether (50 mL) was added and the observed precipitate recovered by filtration and dried under vacuum to give the title compound (113mg, 62%) as a solid.

^{1}H NMR δ: 3.25m (t,1H), 3.6 (m,3H), 4.0 (m,1H), 4.2 (m,1H), 4.5 (m,1H), 7.85 (d,1H), 8.7 (d,1H), 8.8(s,1H), 9.0 (bs,3H); MS m/z 208.

Intermediate 3: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)carbamate

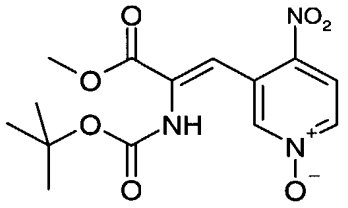


Methyl 2-*tert*-butoxycarbonylamino-3-(4-nitro-1-oxy-pyridin-3-yl)-acrylate (**Intermediate 4,** 1.08 g, 3.18 mmol) was dissolved in ethanol (100 mL) and palladium on carbon catalyst (200 mg, 10% w/w) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 72 hours. After removing the catalyst by filtration through Celite, the

filtrate was concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica gel eluting with 5% methanol in DCM to give the title compound (380 mg, 45%) as a solid.

^{1}H NMR δ: 1.4 (s,9H); 3.0 (m,2H); 4.2 (m,1H); 6.8 (d,1H), 7.0 (bd,1H); 8.25 (d,1H); 8.3 (s,1H); 10.5 (s,1H); MS m/z 264.

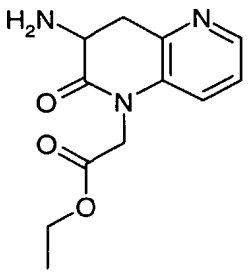
Intermediate 4: Methyl 2-*tert*-butoxycarbonylamino-3-(4-nitro-1-oxy-pyridin-3-yl)-acrylate



Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.633g, 5.5 mmol) was dissolved in dry THF (30 mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (603 mg, 5.25 mmol) was added and the solution stirred at –78 °C for a further 15mins. A slurry of 4-Nitronicotinaldehyde-*N*-oxide (Eur.J.Med.Chem. 2000, *35(1)*, 77-82, 850 mg, 5 mmol), in dry THF (5 mL) was added and stirred at –78 °C for 3 hours. Water (100 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with water (2 x 20mL) and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was triturated with ether to give the title compound (1.08g, 64%) as a yellow solid.

^{1}H NMR δ: 1.3 (s, 9H); 3.8 (s, 3H); 7.1 (s, 1H); 8.15 (m, 2H); 8.35 (d, 1H); 8.85 (s,1H); MS m/z 338 (M-H).

Intermediate 5: Ethyl (3-amino-2-oxo-3,4-dihydro-1,5-naphthyridin-1(2*H*)-yl)acetate dihydrochloride



Sodium hydride (128 mg, 60% dispersion in mineral oil, 3.2mmol) was added to a solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl)carbamate (**Intermediate 15,** 700 mg, 2.7mmol) in DMF (10 mL). The mixture was stirred under nitrogen at ambient temperature for 0.5 hours and then ethyl bromoacetate (0.32 mL, 2.9 mmol) was added. Stirring was continued for a further 18 hour. The reaction mixture was diluted water (20 mL) and extracted with ethyl acetate (3 x 20 mL). The combined extracts were washed with water (2 x 20 mL) and brine (20 ml), dried ($MgSO_4$) and evaporated. The crude material was purified by flash column chromatography on silica gel eluting with a DCM/methanol gradient (0-2%) to give a foam. This material was dissolved in DCM (30 mL), treated with 4.0M HCl in dioxane (20 mL) and stirred at ambient temperature for 2 hours. Ether (50 mL) was added and the resulting precipitate recovered by filtration and dried under vacuum to give the title compound (698 mg, 80%) as a white solid.

^{1}H NMR δ: 1.2 (t,3H), 3.4 (m,2H), 4.1 (q,2H), 4.5 (m,1H), 4.7 (d,1H), 4.9 (d,1H), 7.5 (m,1H), 7.7 (d,1H), 8.3(d,1H), 8.9 (bs,3H); MS m/z 250.

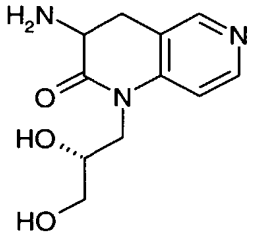
Intermediate 6: 3-Amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride

Sodium hydride (205 mg, 60% dispersion in mineral oil, 5.14 mmol) was added to a solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl)carbamate (**Intermediate 15,** 1.35 g, 5.14 mmol) in DMF (20 mL). The mixture was stirred under nitrogen at ambient temperature for 0.5 hours and then [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl methanesulfonate (1.295 g, 6.16 mmol) was added. The mixture was heated at 80 °C for 18 hours. After cooling to ambient temperature the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with water (2 x 25 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The crude material was purified by flash column chromatography on silica gel eluting ethyl acetate to give a clear oil. 1g of this material was dissolved in DCM (10 mL), treated with 4.0M HCl in dioxane (10 mL) and stirred at ambient temperature for 2 hours. Ether (80 mL) was added and the observed

precipitate recovered by filtration and dried under vacuum to give the title compound (800 mg, 98%) as a yellow solid.

^{1}H NMR δ: 3.45 (m,4H), 3.75 (m,2H), 4.05 (m,2H), 7.5 (m,1H), 7.7 (d,1H), 8.3(d,1H), 8.9 (bs,3H); MS m/z 238.

Intermediate7: 3-Amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one dihydrochloride



Prepared from *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)carbamate (**Intermediate 3**; 826 mg, 3.14 mmol) and [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl methanesulfonate (725 mg, 3.45 mmol) by the same process used for **Intermediate 6.**

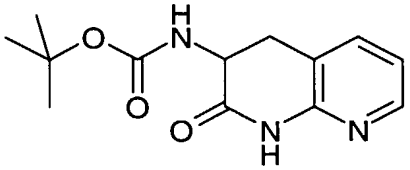
^{1}H NMR δ: 3.25 (m,1H), 3.4 (m,2H), 3.6(m1H), 3.8 (m,1H), 3.9 (m,1H), 4.1 (d,1H), 4.2 (d,1H), 4.3(b,1H), 4.5 (b,1H), 7.9 (d,1H), 7.7 (m,1H), 8.85(s,1H), 9.0 (bs,3H); MS m/z 238.

Intermediate 8: 3-Amino-1-[(2*R*)-2,3-dihydroxypropyl]-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one dihydrochloride

Prepared from *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl)carbamate (**Intermediate 9**, 872 mg, 3.3 mmol) and [(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl methanesulfonate (76 mg, 3.6 mmol) by the same process used for **Intermediate 6.**

^{1}H NMR δ: 3.2 (m,4H), 3.9 (m, 2H), 4.25 (m, 2H), 7.1 (m,1H), 7.8 (m,1H), 8.3(m,1H), 9.0 (bs, 3H); MS M/z 238.

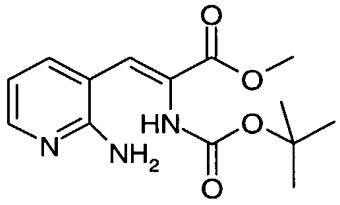
Intermediate 9: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl)carbamate



Methyl (2*Z*)-3-(2-aminopyridin-3-yl)-2-[(*tert*-butoxycarbonyl)amino]acrylate (**Intermediate 10,** 3.17 g, 10.8 mmol) was suspended in ethanol (200 mL) and palladium on carbon catalyst (500 mg, 10% w/w) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 24 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a white solid which was purified by chromatography on silica gel eluting with isohexane containing an increasing proportion of ethyl acetate (0-100%). After removing the volatiles by evaporation under reduced pressure the resulting solid was triturated with ether and the product collected by filtration to give the title compound (1.3 g, 46%) as a solid.

^{1}H NMR δ: 1.4 (s,9H); 3.0 (m,2H); 4.2 (m,1H); 6.9 (m,2H), 7.6 (d,1H); 8.1 (d,1H), 10.7 (s,1H); MS m/z 264.

Intermediate 10: Methyl (2*Z*)-3-(2-aminopyridin-3-yl)-2-[(*tert*-butoxycarbonyl)amino]acrylate

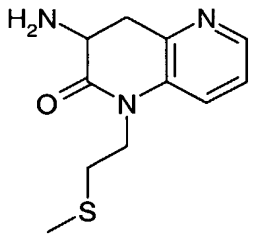


Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (5.47g , 18.0 mmol) was dissolved in dry THF (135 mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (2.42 mL, 19.0 mmol) was added and the solution stirred at –78°C for a further 15 mins. A solution 2-aminonicotinaldehyde (2.25 g, 18 mmol) in dry THF (50 mL) was then added dropwise . After the addition was complete stirring was continued at ambient temperature for a further 18 hours. The solution was then diluted with water (100 mLl) and extracted with ethyl acetate (3 x 100mL). The combined extracts were washed with water (2 x 100mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow solid. This was further purified by chromatography on silica gel eluting with isohexane containing

an increasing proportion of ethyl acetate (50-100%) to give the title compound (3.19g, 59%) as a yellow solid.

^{1}H NMR δ: 1.4 (s, 9H); 3.7 (m, 3H); 6.05 (s, 2H); 6.6 (m, 1H); 7.0 (bs, 1H); 7.6 (d,1H); 7.9 (d,1H), 8.5 (bs,1H); MS m/z 394.

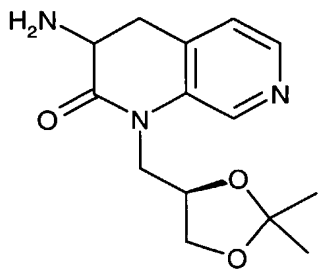
Intermediate 11: 3-Amino-1-[2-(methylthio)ethyl]-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride



Sodium hydride (84 mg, 60% dispersion in mineral oil, 2.1 mmol) was added to a solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl)carbamate (**Intermediate 15,** 500 mg, 1.9 mmol) in DMF (10 mL). The mixture was stirred under nitrogen at ambient temperature for 0.5 hours and then 2-chloroethyl methyl sulfide (0.19 mL, 1.9mmol) was added. The mixture was heated at 80 °C for 18 hours. After cooling to ambient temperature the reaction mixture was diluted water (20 mL) and extracted with ethyl acetate (3 x 20mLl). The combined extracts were washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated. The crude material was purified by flash column chromatography on silica gel eluting with DCM containing an increasing proportion of ethyl acetate (0-70%) to give an oil. This material was dissolved in DCM (15 mL), treated with 4.0M HCl in dioxane (15 mL) and stirred at ambient temperature for 2 hours. Ether (80 mL) was added and the observed precipitate was recovered by filtration and dried under vacuum to give the title compound (364 mg, 79%) as a pale yellow solid.

^{1}H NMR δ: 2.1 (s,3H), 2.7 (t,2H), 3.45 (t,1H), 3.65 (m,1H), 4.2 (t,2H), 4.5(m,1H), 7.6 (m,1H), 7.95 (d,1H), 8.35 (d,1H), 8.9 (bs,3H); MS m/z 238.

Intermediate 12: (*3R/S*)-3-Amino-1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one



4-Methyl-nitropyridine (1.43 g, 10.36mmol) was dissolved in dry DMF (5mL) and dimethylformamide dimethyl acetal (2.0 g, 16.8 mmol) was added. The mixture was heated under nitrogen at 140°C for 2 hours and then evaporated under reduced pressure to give (*E*)-*N,N*-dimethyl-2-(3-nitropyridin-4-yl)ethyleneamine as a dark red solid. This was added in one portion at ambient temperature to a stirred solution of sodium periodate (6.61 g, 31 mmol) in THF/ Water 1:1 (100 mL). After stirring for 2hr at ambient temperature the reaction mixture was filtered and the solid washed with ethyl acetate (100 mL). The washings were combined with the filtrate and organic layer separated. The aqueous was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown solid which was purified by column chromatography (DCM) to give 3-nitroisonicotinaldehyde (960mg, 61%).

^{1}H NMR δ: 7.8 (d, 1H); 9.15 (d, 1H); 9.4(s, 1H); 10.4 (s, 1H)

Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.73g, 5.82 mmol) was dissolved in dry THF (20 mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (638 mg, 5.55 mmol) was added and the solution stirred at –78 °C for a further 10 mins. A solution of 3-nitroisonicotinaldehyde (804 mg, 5.29 mmol) in dry THF (5mL) was added dropwise. The resulting deep red solution was stirred for 2hrs at –78°C, then poured into a mixture of ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (EtOAc: *iso*hexane 1:1) to give methyl-2-[(tert-butoxycarbonyl)amino]-3-(3-nitropyridin-4-yl)acrylate as a 10:1 mixture of Z/E isomers (1.57g, 92%).

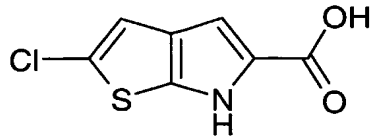
^{1}H NMR δ: 1.3 (s, 9H); 1.4 (s, 0.9H); 3.55 (s, 0.3H); 3.8 (s, 3H); 6.6 (s, 0.1H); 7.2 (s, 1H); 7.25(d, 0.1H); 7.5 (d, 1H); 8.75 (d, 0.1H); 8.8 (s, 1.1H); 8.85 (d, 1H); 9.2 (s, 0.1H); 9.25 (s, 1H); MS m/z 322.

Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-4-yl)acrylate (10:1 mixture of Z/E isomers) (1.57 g , 4.83 mmol) was dissolved in ethanol and 10% palladium on carbon catalyst (250 mg) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 6 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a yellow oil which was purified by column chromatography (Eluent DCM / MeOH gradient 0-10%) to give tert-butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate (284mg, 22%).
^{1}H NMR δ: 1.4 (s, 9H); 3.0 (m, 2H); 4.2 (m, 1H); 7.0 (d , 1H); 7.2 (d,1H); 8.1 (m, 2H); 10.36 (s, 1H); MS m/z 264.

tert-Butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate (284mg) was dissolved in DCM (10 mL) and treated with trifluoroacetic acid (5 mL). After stirring at ambient temperature for 1 hour the reaction mixture was evaporated under reduced pressure and the residue triturated with ether (20 mL) to give a light brown solid which was collected by filtration, washed with ether and dried to give 3-amino-3,4-dihydro-1,7-naphthyridin-2(1H)-one (346 mg, 82%)as a bis trifluroacetate salt.
^{1}H NMR δ: 3.2 (m, 2H); 4.3 (m, 1H), 7.4 (d, 1H); 8.2 (s, 1H); 8.25 (d, 1H); 8.6 (b, 3H); 11.0 (s, 1H)

Sodium hydride (1.18 g, 60% dispersion in oil, 29.4 mmol) was added to a suspension of (3*R/S*)-3-Amino-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one (2.24 g, 9.4 mmol) in dry DMF (40 mL) and the mixture heated to 80 °C and stirred for 30 mins. [(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]methyl methanesulfonate (2 mL, 10.4 mmol) was added and the reaction stirred at 80 °C for 19 h. The mixure was cooled, diluted with DCM (450 mL), purified using flash column chromatography (SiO_2, eluent: DCM to DCM:MeOH, 85:15 to DCM:MeOH:NH_4OH, 80:20:0.7) and the volatiles removed under reduced pressure to afford the title compound (1.1 g, 42%) as an oil.
^{1}H NMR δ: 1.23 (m, 3H), 1.26 (s, 1.8H), 1.28 (s, 1.2H), 3.52 (m, 1H), 3.68 (m, 1H), 4.02 (m, 2H), 4.15 (m, 1H), 4.31 (m, 1H), 7.27 (br d, 1H), 8.21 (d, 1H), 8.55 (d, 1H); MS m/z 278.

Intermediate 13: 2-Chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid



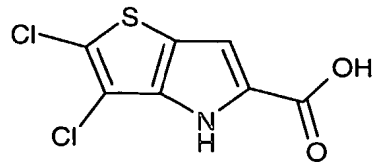
Sodium (659 mg, 28.7 mL) was added to dry methanol (20 mL) and the mixture stirred at ambient temperature for 30 mins before cooling to –20 °C. 2-Chlorothiophene-3 – carboxaldehyde (Gronowitz *et al.*, Tetrahedron Vol.32 1976 p.1403; 1.17 g, 7.2 mmol) and methyl azidoacetate (3.3 g, 28.7 mmol) were added as a methanol (10 mL) solution and the reaction was stirred from –20 °C to 10 °C over 16 hours. The reaction was poured on saturated aqueous ammonium chloride solution (300 mL) and extracted with DCM (3 x 100 mL). The combined organic phases were washed with water (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was redissolved in xylene (50 mL) and added dropwise to refluxing xylene (150 mL) and stirred for at reflux for a further 30 mins after the addition was complete. The solvent was removed under reduced pressure to afford a yellow solid which was recrystallised (25:75, EtOAC:*iso*-hexane) to afford 2-chloro-5-methoxycarbonyl-6H-thieno[2,3-b]pyrrole (1.06 g, 69%) as a solid.

^{1}H NMR ($CDCl_3$) δ: 9.4-9.2 (1H, br), 7.0 (1H, s), 6.9(1H, s), 3.9 (3H, s); m/z 214, 216

Sodium hydroxide (2N, 15 mL) was added to a methanol (50 mL) solution of 2-chloro-5-methoxycarbonyl-6*H*-thieno[2,3-*b*]pyrrole (777 mg, 3.6 mmol) and the mixture heated at reflux for 5 hours. The reaction was cooled to ambient temperature, water (250 mL) added and the aqueous phase was washed with Et_2O (2 x 50 mL), acidified to pH 2 with HCl (2N) and extracted with EtOAc (3 x 50 mL). The combined organic phases were washed with water (2 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the title compound (705 mg, 97%) as a pale pink solid.

^{1}H NMR ($CDCl_3$) δ: 12.6-12.7 (1H, b), 12.0-12.1 (1H, b), 7.15 (1H, s), 6.9 (1H, s); m/z 183, 185.

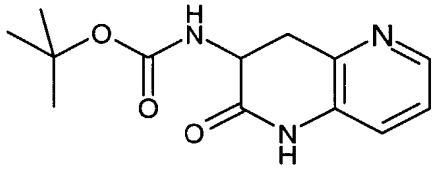
Intermediate 14: 2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid



Starting from 4,5-dichlorothiophene-2-carbaldehyde (DE 2814798) and using a similar procedure to that described above for the preparation of 2-chloro-6H-thieno[2,3-b]pyrrole-5-carboxylic acid (**Intermediate 13**) afforded, via methyl 2,3-dichloro-4H-thieno[3,2-b]pyrrole-5-carboxylate, ^{1}H NMR ($CDCl_3$) δ: 9.2 (1H, br), 7.0 (1H, s), 3.9 (3H, s); m/z 248.2), the title compound:

^{1}H NMR ($CDCl_3$) δ: 7.0 (1H, s); MS m/z 234.2

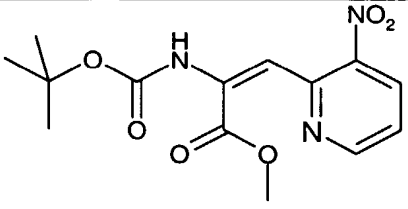
Intermediate 15: *tert*-Butyl(2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridine-3-yl)carbamate



Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-2-yl)acrylate (4:1 mixture of Z/E isomers) (**Intermediate 16,** 1.1 g, 3.4 mmol) was dissolved in ethanol and palladium on carbon catalyst (250mg, 10% w/w) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 12 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a yellow oil. The oil was dissolved in methanol (20 mL) and treated with a 0.5M solution of sodium methoxide in methanol (8 mL). After stirring at ambient temperature for 4 hrs. the mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with water (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid (528mg, 59%)

^{1}H NMR δ: 1.4 (s, 9H); 3.1 (m, 2H); 4.3 (m, 1H); 7.0 (bd, 1H); 7.2 (m, 2 H); 8.1 (t, 1H); 10.26 (s, 1H); MS m/z 208.

Intermediate 16: Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-2-yl)acrylate



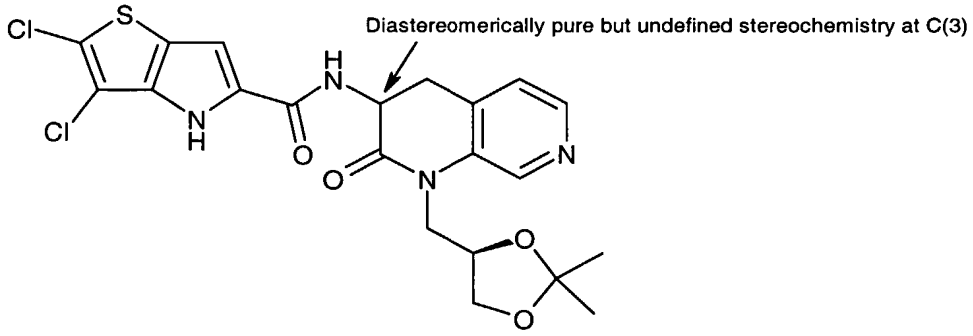
Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.33g , 4.46 mmol.) was dissolved in dry THF (20mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (490 mg, 4.26 mmol.) was added and the solution stirred at –78 °C for a further 10 mins. A

solution of 3-nitropyridine-2-carbaldehyde (Tetrahedron vol .54 (1998) p 6311, 618 mg, 4.06 mmol) in dry THF (5 mL) was added dropwise. After stirring the solution for 2 hours at –78°C it was diluted with water (150 mL) and extracted with ethyl acetate (2 x 50mL). The combined extracts were washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (SiO_2, DCM) to give the title compound (1.1g, 84%) as a 4:1 mixture of Z/E isomers.

^{1}H NMR δ: 1.4 (s, 11.25H); 3.6 (s, 0.75H); 3.8 (s, 3H); 6.7 (s, 1H); 6.9 (s, 0.25H); 7.45 (m, 0.25H), 7.6 (m, 1H); 8.37 (d, 0.25H); 8.5 (d, 1H); 8.7 (d, 0.25H); 8.9 (d, 1H); 9.8 (s, 0.25H); 10.3 (s, 1H); MS m/z 322.

Intermediate 17: (3*R* or *S*)-2,3-Dichloro-*N*-(1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

Intermediate 18: (3*S* or *R*)-2,3-Dichloro-*N*-(1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide

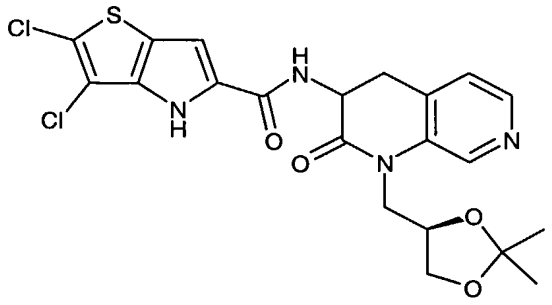


(3*R*/*S*)-2,3-Dichloro-*N*-(1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide (**Intermediate 19**; 1.2 g, 2.4 mmol) was subjected to the same chromatographic separation as that used for **Examples 8 and 9,** to afford the first eluted isomer A (**Intermediate 17**; 576 mg, 48%) and second eluted isomer isomer B (**Intermediate 18**; 474 mg, 39%).

Intermediate 17 first eluted component - Isomer A: ^{1}H NMR δ: 1.24 (d, 6H), 3.2 (m, 2H), 3.7 (dd, 1H), 4.1 (m, 2H), 4.25 (d, 1H), 4.35 (m, 1H), 4.8 (m, 1H), 7.2 (s, 1H), 7.3 (d, 1H), 8.25 (d, 1H), 8.63 (s, 1H), 8.65 (d, 1H), 12.53 (s, 1H); MS m/z 493 (M-H).

Intermediate 18 second eluted component - Isomer B: ^{1}H NMR δ: 1.24 (d, 6H), 3.15 (m, 2H), 3.7 (dd, 1H), 3.95 (m, 1H), 4.2 (m, 2H), 4.33 (m, 1H), 4.78 (m, 1H), 7.2 (s, 1H), 7.33 (d, 1H), 8.25 (d, 1H), 8.65 (m, 2H), 12.5 (br s, 1H); MS m/z 493 (M-H).

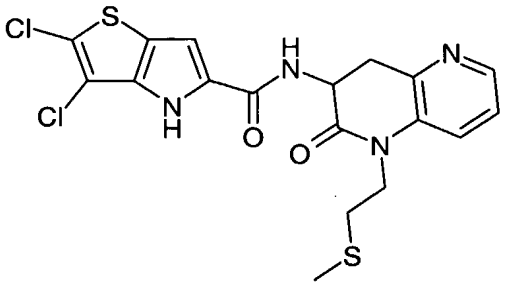
Intermediate 19: (3*R/S*)-2,3-Dichloro-*N*-(1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridin-3-yl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



(*3R/S*)-3-Amino-1-{[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one (**Intermediate 12**; 1.1 g, 3.97 mmol) was dissolved in DMF (30 mL) and the solution degassed by bubbling nitrogen gas through it for 5 mins. 2,3-Dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 0.94 g, 3.97 mmol), HOBT (0.54 g, 3.97 mmol) and EDCI (0.76 g, 3.97 mmol) were added and the reaction stirred at ambient temperature for 5.5 h. The reaction was poured onto saturated aqueous sodium bicarbonate (250 mL) and the resulting precipitate was filtered, re-dissolved in EtOAc (100 mL), dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography (SiO_2, EtOAc to EtOAc:MeOH, 9:1) afforded the title compound (1.69 g, 86%) as a yellow solid.

^{1}H NMR δ: 1.24 (m, 6H), 3.17 (m, 1H), 3.72 (dd, 1H), 4.39-4.01 (m, 5H), 4.78 (m, 1H), 7.21 (d, 1H), 7.33 (d, 1H), 8.26 (d, 1H), 8.62 (s, 1H), 8.65 (m, 2H), 12.52 (s, 1H); MS m/z 493 (M-H).

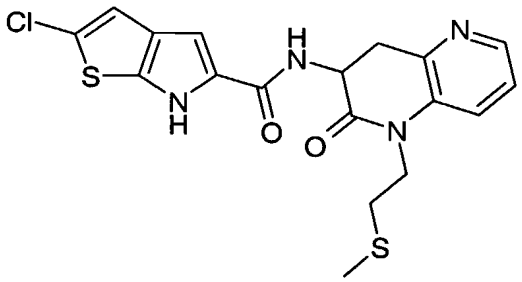
Intermediate 20: 2,3-Dichloro-*N*-{1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-4*H*-thieno[3,2-*b*]pyrrole-5-carboxamide



Prepared from 2,3-dichloro-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylic acid (**Intermediate 14,** 127mg, 20.54mmol) and 3-amino-1-[2-(methylthio)ethyl]-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 11**, 167mg, 0.54mmol) by a similar process to that used for **Example 1**.

^{1}H NMR δ: 2.1 (s,3H), 2.7 (t,2H), 3.2 (m,1H), 3.4 (m,2H), 4.1 (m,2H), 4.9 (m,1H), 7.2 (s,1H), 7.3 (m,1H), 7.4 (d,1H), 8.2 (d,1H), 8.6(d,1H), 12.5 (s,1H); MS m/z 455, 453 (M-H).

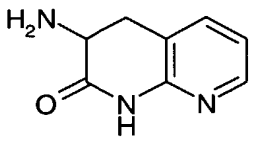
Intermediate 21: 2-Chloro-*N*-{1-[2-(methylthio)ethyl]-2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridin-3-yl}-6*H*-thieno[2,3-*b*]pyrrole-5-carboxamide



Prepared from 2-chloro-6*H*-thieno[2,3-*b*]pyrrole-5-carboxylic acid (**Intermediate 13,** 109 mg, 0.54 mmol), and 3-amino-1-[2-(methylthio)ethyl]-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride (**Intermediate 11**, 167 mg, 0.54 mmol) by a similar process to that used for **Example 1**.

^{1}H NMR δ: 2.1 (s,3H), 2.7 (m,2H), 3.15 (t,1H), 3.85 (dd,1H), 4.2 (m,2H), 4.9 (m,1H), 6.8 (s,1H), 6.85(s,1H), 7.2 (d,1H), 7.3 (m,1H), 7.4 (d,1H), 8.35(d,1H), 10.44 (s,1H); MS m/z 421, 419 (M-H).

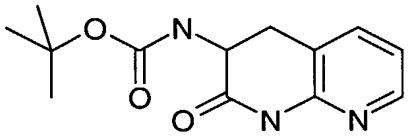
Intermediate 22: 3-Amino-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one



Prepared from **Intermediate 23** following the method described below for the conversion of **Intermediate 30** into **Intermediate 29**.

^{1}H NMR ($CDCl_3$) δ: 2.90 (t, 1H), 3.15 (dd, 1H), 4.70 (m, 1H), 7.00 (m, 1H), 7.50 (d, 1H), 8.30 (d, 1H), 9.85 (br s, 1H); MS: 164 $(M+H)^+$.

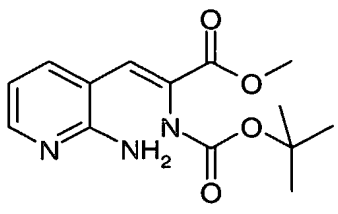
Intermediate 23: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,8-naphthyridin-3-yl)carbamate



Methyl (2*Z*)-3-(2-aminopyridin-3-yl)-2-[(*tert*-butoxycarbonyl)amino]acrylate (**Intermediate 24,** 3.17g, 10.8 mmol) was suspended in ethanol (200 mL) and palladium on carbon catalyst (500 mg, 10% w/w) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 24 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a white solid which was purified by chromatography on silica gel eluting with isohexane containing an increasing proportion of ethyl acetate (0-100%). The volatiles were evaporated under reduced pressure, then the resulting solid was triturated with ether and the product collected by filtration to give the title compound (1.3 g, 46%) as a solid.

^{1}H NMR δ: 1.4 (s,9H); 3.0 (m,2H); 4.2 (m,1H); 6.9 (m,2H), 7.6 (d,1H); 8.1 (d,1H), 10.7 (s,1H); MS: 264.

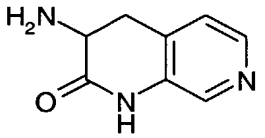
Intermediate 24: Methyl (2*Z*)-3-(2-aminopyridin-3-yl)-2-[(*tert*-butoxycarbonyl)amino] acrylate



Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (5.47g , 18.0 mmol) was dissolved in dry THF (135 mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (2.42 mL, 19.0 mmol) was added and the solution stirred at –78°C for a further 15 mins. A solution 2-aminonicotinaldehyde (2.25 g, 18 mmol) in dry THF (50 mL) was then added dropwise . After the addition was complete stirring was continued at ambient temperature for a further 18 hours. The solution was then diluted with water (100 mL) and extracted with ethyl acetate (3 x 100 mL). The combined extracts were washed with water (2 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow solid. This was further purified by chromatography on silica gel eluting with isohexane containing an increasing proportion of ethyl acetate (50-100%) to give the title compound (3.19g, 59%) as a yellow solid.

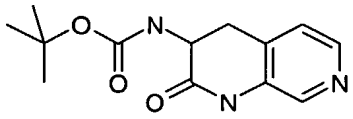
^{1}H NMR δ: 1.4 (s, 9H); 3.7 (m, 3H); 6.05 (s, 2H); 6.6 (m, 1H); 7.0 (bs, 1H); 7.6 (d,1H); 7.9 (d,1H), 8.5 (bs,1H); MS: 394.

Intermediate 25: 3-Amino-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one dihydrochloride



Prepared from **Intermediate 26** following the method described below for the conversion of **Intermediate 30** into **Intermediate 29**. ^{1}H NMR δ: 3.35 (m, 1H), 3.50 (m, 1H), 4.35 (m, 1H), 7.80 (d, 1H), 8.35 (s, 1H), 8.40 (d, 1H), 8.85 (br s, 3H), 11.40 (br s, 1H); MS: 164 $(M+H)^+$.

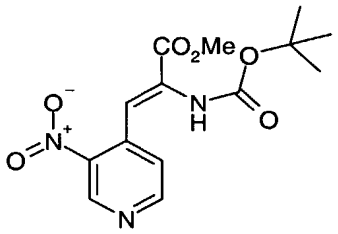
Intermediate 26: tert-Butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate



Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3-nitropyridin-4-yl)acrylate (**Intermediate 27**,10:1 mixture of Z/E isomers) (1.57 g , 4.83 mmol) was dissolved in ethanol and 10% palladium on carbon catalyst (250 mg) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 6 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a yellow oil which was purified by column chromatography (Eluent DCM / MeOH gradient 0-10%) to give *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate (284 mg, 22%).

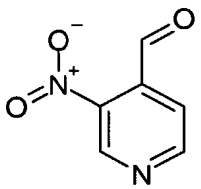
^{1}H NMR δ: 1.4 (s, 9H); 3.0 (m, 2H); 4.2 (m, 1H); 7.0 (d , 1H); 7.2 (d,1H); 8.1 (m, 2H); 10.36 (s, 1H); MS: 264.

Intermediate 27: Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-4-yl)acrylate



Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.73g, 5.82 mmol) was dissolved in dry THF (20mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (638 mg, 5.55 mmol) was added and the solution stirred at –78 °C for a further 10 mins. A solution of 3-nitroisonicotinaldehyde (**Intermediate 28,** 804 mg, 5.29 mmol) in dry THF (5mL) was added dropwise. The resulting deep red solution was stirred for 2hrs. at –78°C, then poured into a mixture of ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (EtOAc: *iso*hexane 1:1) to give methyl-2-[(tert-butoxycarbonyl)amino]-3-(3-nitropyridin-4-yl)acrylate as a 10:1 mixture of Z/E isomers (1.57g, 92%).
^{1}H NMR δ: 1.3 (s, 9H); 1.4 (s, 0.9H); 3.55 (s, 0.3H); 3.8 (s, 3H); 6.6 (s, 0.1H); 7.2 (s, 1H); 7.25(d, 0.1H); 7.5 (d, 1H); 8.75 (d, 0.1H); 8.8 (s, 1.1H); 8.85 (d, 1H); 9.2 (s, 0.1H); 9.25 (s, 1H); MS: 322.

Intermediate 28: 3-Nitroisonicotinaldehyde

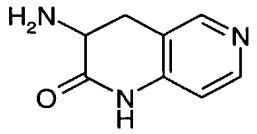


4-Methyl-3-nitropyridine (1.43 g, 10.36 mmol) was dissolved in dry DMF (5 mL) and dimethylformamide dimethyl acetal (2.0 g, 16.8 mmol) was added. The mixture was heated under nitrogen at 140^{0}C for 2 hours and then evaporated under reduced pressure to give (*E*)-*N,N*-dimethyl-2-(3-nitropyridin-4-yl)ethyleneamine as a dark red solid. This was added in one

portion at ambient temperature to a stirred solution of sodium periodate (6.61g, 31mmol) in THF/ Water 1:1 (100 mL). After stirring for 2hr at ambient temperature the reaction mixture was filtered and the solid washed with ethyl acetate (100 mL). The washings were combined with the filtrate and organic layer separated. The aqueous was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown solid which was purified by column chromatography (DCM) to give 3-nitroisonicotinaldehyde (960 mg, 61%).

^{1}H NMR δ: 7.8 (d, 1H); 9.15 (d, 1H); 9.4(s, 1H); 10.4 (s, 1H)

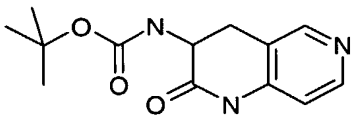
Intermediate 29: 3-Amino-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one dihydrochloride



.2 HCl

To a stirred solution of *tert*-butyl (2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)carbamate (**Intermediate 30**; 1.24 g, 4.7 mmol) in dioxane (10 mL) was added a 4M solution of HCl in dioxane (60 mL). The reaction was stirred at room temperature for 48 hours then evaporated under reduced pressure to yield a solid. This solid was dried under vacuum for 3 hours to yield the product as the dihydrochloride salt (1.2 g, 109 %). ^{1}H NMR δ: 3.25 (t, 1H), 3.50 (m, 1H), 4.45 (m, 1H), 7.40 (d, 1H), 8.60 (d, 2H), 8.80 (s, 1H), 8.95 (br s, 4H), 12.20 (s, 1H); MS: 164 $(M+H)^+$.

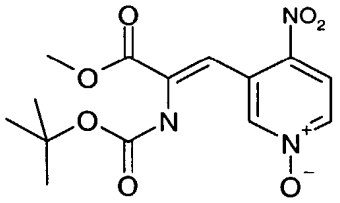
Intermediate 30: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,6-naphthyridin-3-yl)carbamate



3-[2-(*tert*-Butoxycarbonylamino)-2-(methoxycarbonyl)ethenyl]4-nitropyridin-1-oxide (**Intermediate 31**, 1.08 g, 3.18 mmol) was dissolved in ethanol (100 mL) and palladium on carbon catalyst (200 mg, 10% w/w) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 72 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a yellow oil which was purified by chromatography on silica gel eluting with 5% methanol in DCM to give the title compound (380 mg, 45%) as a solid.

^{1}H NMR δ: 1.4 (s,9H); 3.0 (m,2H); 4.2 (m,1H); 6.8 (d,1H), 7.0 (bd,1H); 8.25 (d,1H); 8.3 (s,1H); 10.5 (s,1H); MS: 264.

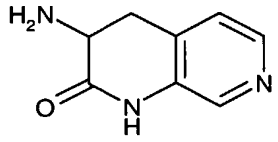
Intermediate 31: 3-[2-(*tert*-Butoxycarbonylamino)-2-(methoxycarbonyl)ethenyl]-4-nitropyridine-1-oxide



Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.633 g, 5.5 mmol) was dissolved in dry THF (30 mL) and cooled to –78 °C under nitrogen. Tetramethylguanidine (603 mg, 5.25 mmol) was added and the solution stirred at –78 °C for a further 15mins. A slurry of 4-nitronicotinaldehyde-*N*-oxide (Eur.J.Med.Chem. 2000, *35(1)*, 77-82, 850 mg, 5 mmol), in dry THF (5 mL) was added and stirred at –78 °C for 3 hours. Water (100 mL) was added and the aqueous phase was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was triturated with ether to give the title compound (1.08 g, 64%) as a yellow solid.

^{1}H NMR δ: 1.3 (s, 9H); 3.8 (s, 3H); 7.1 (s, 1H); 8.15 (m, 2H); 8.35 (d, 1H); 8.85 (s,1H); MS: 338 $(M-H)^+$.

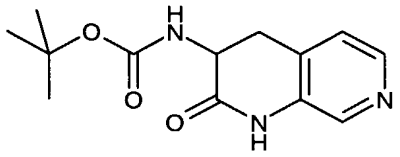
Intermediate 32: 3-Amino-3,4-dihydro-1,7-naphthyridin-2(1*H*)-one



tert-Butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate (**Intermediate 33**, 284 mg) was dissolved in DCM (10 mL) and treated with trifluoroacetic acid (5 mL). After stirring at ambient temperature for 1 hour the reaction mixture was evaporated under reduced pressure and the residue triturated with ether (20 mL), to give a light brown solid which was collected by filtration, washed with ether and dried to give the title compound (346mg, 82%) as a bis trifluroacetate salt.

^{1}H NMR δ: 3.2 (m, 2H); 4.3 (m, 1H), 7.4 (d, 1H); 8.2 (s, 1H); 8.25 (d, 1H); 8.6 (b, 3H); 11.0 (s, 1H)

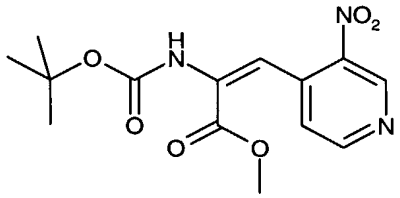
Intermediate 33: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,7-naphthyridine-3-yl)carbamate



Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-4-yl)acrylate (10:1 mixture of Z/E isomers) (**Intermediate 34**,1.57 g , 4.83mmol) was dissolved in ethanol and 10% palladium on carbon catalyst (250 mg) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 6 hours. After removing the catalyst by filtration through Celite the filtrate was concentrated under reduced pressure to give a yellow oil which was purified by column chromatography (Eluent DCM / MeOH gradient 0-10%) to give the title compound (284mg, 22%).

^{1}H NMR δ: 1.4 (s, 9H); 3.0 (m, 2H); 4.2 (m, 1H); 7.0 (d , 1H); 7.2 (d,1H); 8.1 (m, 2H); 10.36 (s, 1H); MS m/z 264.

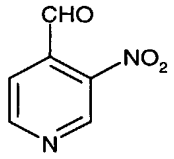
Intermediate 34: Methyl-2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-4-yl)acrylate



Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.73g, 5.82 mmol) was dissolved in dry THF (20 mL) and cooled to –78°C under nitrogen. Tetramethylguanidine (638mg, 5.55 mmol) was added and the solution stirred at –78°C for a further 10 mins. A solution of 3-nitroisonicotinaldehyde (**Intermediate 35,** 804 mg, 5.29 mmol) in dry THF (5 mL) was added dropwise. The resulting deep red solution was stirred for 2hrs. at –78°C, then poured into a mixture of ethyl acetate (100 mL) and water (50 mL). The organic layer was separated, washed with water (2 x 50 mL) and brine (25 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (EtOAc: *iso*hexane 1:1) to give the title compound as a 10:1 mixture of Z/E isomers (1.57g, 92%).

^{1}H NMR δ: 1.3 (s, 9H); 1.4 (s, 0.9H); 3.55 (s, 0.3H); 3.8 (s, 3H); 6.6 (s, 0.1H); 7.2 (s, 1H); 7.25(d, 0.1H); 7.5 (d, 1H); 8.75 (d, 0.1H); 8.8 (s, 1.1H); 8.85 (d, 1H); 9.2 (s, 0.1H); 9.25 (s, 1H); MS m/z 322.

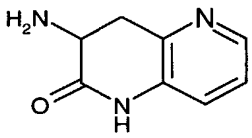
Intermediate 35: 3-Nitroisonicotinaldehyde



4-Methyl-nitropyridine (1.43 g, 10.36 mmol) was dissolved in dry DMF (5 mL) and dimethylformamide dimethyl acetal (2.0 g, 16.8 mmol) was added. The mixture was heated under nitrogen at 140°C for 2 hours and then evaporated under reduced pressure to give (*E*)-*N,N*-dimethyl-2-(3-nitropyridin-4-yl)ethyleneamine as a dark red solid. This was added in one portion at ambient temperature to a stirred solution of sodium periodate (6.61 g, 31 mmol) in THF/ water 1:1 (100 mL). After stirring for 2hr at ambient temperature the reaction mixture was filtered and the solid washed with ethyl acetate (100 mL). The washings were combined with the filtrate and organic layer separated. The aqueous was extracted with ethyl acetate (2 x 100 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate (100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a brown solid which was purified by column chromatography (DCM) to give the title compound. (960 mg, 61%).

^{1}H NMR δ: 7.8 (d, 1H); 9.15 (d, 1H); 9.4(s, 1H); 10.4 (s, 1H)

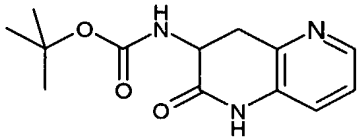
Intermediate 36: 3-Amino-3,4-dihydro-1,5-naphthyridin-2(1*H*)-one dihydrochloride



tert-Butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridine-3-yl)carbamate (**Intermediate 37**, 263 mg, 1 mmol) was dissolved in DCM (10 mL) and treated with 4M HCl in dioxane (10 mL). After stirring at ambient temperature for 30 mins. The reaction mixture was evaporated under reduced pressure and the residue triturated with ether (20 mL), to give a white solid which was collected by filtration, washed with ether and dried. (234 mg, 100%).

^{1}H NMR δ: 3.4 (m, 1H); 3.4 (m, 1H); 4.5 (m, 1H); 7.5 (m, 2H); 8.3 (d, 1H); 8.75 (bs, 3H); 11.18 (s, 1H); MS m/z 164

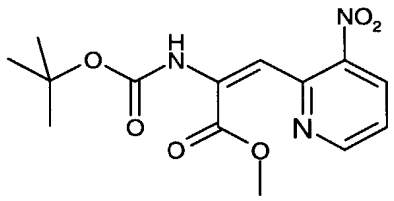
Intermediate 37: *tert*-Butyl (2-oxo-1,2,3,4-tetrahydro-1,5-naphthyridine-3-yl)carbamate



Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-2-yl)acrylate (4:1 mixture of Z/E isomers) (**Intermediate 38,** 1.1 g, 3.4 mmol) was dissolved in ethanol and 10% palladium on carbon catalyst (250 mg) was added. The mixture was stirred under 1 atmosphere of hydrogen at ambient temperature for 12 hours. After removing the catalyst by filtration through Celite, the filtrate was concentrated under reduced pressure to give a yellow oil. The oil was dissolved in methanol (20 mL) and treated with a 0.5M solution of sodium methoxide in methanol (8 mL). After stirring at ambient temperature for 4 hrs. the mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 x 50 mL). The combined extracts were washed with water (2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a white solid (528mg, 59%)

^{1}H NMR δ: 1.4 (s, 9H); 3.1 (m, 2H); 4.3 (m, 1H); 7.0 (bd, 1H); 7.2 (m, 2 H); 8.1 (t, 1H); 10.26 (s, 1H); MS m/z 208.

Intermediate 38: Methyl 2-[(*tert*-butoxycarbonyl)amino]-3-(3nitropyridin-2-yl)acrylate

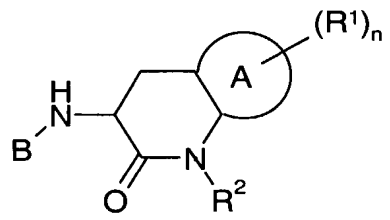


Methyl [(*tert*-butoxycarbonyl)amino](dimethoxyphosphoryl)acetate (1.33 , 4.46 mmol) was dissolved in dry THF (20 mL) and cooled to –78°C under nitrogen. Tetramethylguanidine (490 mg, 4.26 mmol) was added and the solution stirred at –78°C for a further 10 mins. A solution of 3-nitropyridine-2-carbaldehyde (Tetrahedron vol .54 (1998) p 6311) (618 mg, 4.06 mmol) in dry THF (5 mL) was added dropwise. After stirring the solution for 2 hours. at –78°C (50 mL) it was diluted with water (150 mL) and extracted with ethyl acetate . The combined extracts were washed with water (2 x 20 mL) and brine (20 mL), dried ($MgSO_4$) and evaporated under reduced pressure to give a yellow oil, which was purified by column chromatography (DCM) to give the title compound as a 4:1 mixture of Z/E isomers (1.1g, 84%).

^{1}H NMR δ: 1.4 (s, 11.25H); 3.6 (s, 0.75H); 3.8 (s, 3H); 6.7 (s, 1H); 6.9 (s, 0.25H); 7.45 (m, 0.25H), 7.6 (m, 1H); 8.37 (d, 0.25H); 8.5 (d, 1H); 8.7 (d, 0.25H); 8.9 (d, 1H); 9.8 (s, 0.25H); 10.3 (s, 1H); MS m/z 322

Claims

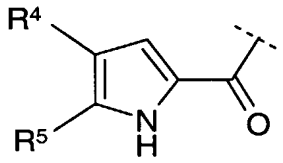
1. A compound of formula (1):



(1)

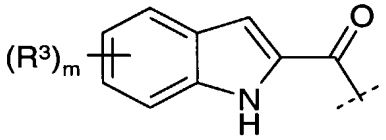
wherein:

B is selected from



(2a)

and



(2b)

R^3 is selected from halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

R^4 and R^5 together are either $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

R^6 and R^7 are independently selected from hydrogen, halo, nitro, cyano, hydroxy, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy, carboxy, carbamoyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy and (1-4C)alkanoyl;

A is a pyridylene ring;

m is 0, 1 or 2;

n is 0 or 1;

when R^1 is a substituent at the 5-position of the pyridyl ring comprising A (using the numbering system described hereinafter), R^1 is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N*,*N*-((1-4C)alkyl)$_2$carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N*,*N*-((1-4C)alkyl)$_2$sulphamoyl, -S(O)$_b$(1-4C)alkyl (wherein b is 0,1,or 2), -OS(O)$_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and $-NHSO_2$(1-4C)alkyl;

when R^1 is a substituent at the 6-, 7- or 8-position of the pyridyl ring comprising A (using the numbering system described hereinafter), R^1 is independently selected from halo, hydroxy, methyl and methoxy;

R^2 is selected from hydrogen, (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-, –(1-4C)alkylNHSO_2(1-4C)alkyl, -(1-4C)alkylSO_2NH(1-4C)alkyl, -(1-4C)alkylSO_2Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl;

or a pharmaceutically acceptable salt or pro-drug thereof.

2. A compound of the formula (1) as claimed in Claim 1, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein B is formula (2a).

3. A compound of the formula (1) as claimed in Claim 2, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein R^6 and R^7 are independently selected from hydrogen and halo

4. A compound of the formula (1) as claimed in Claim 1, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein B is formula (2b).

5. A compound of the formula (1) as claimed in Claim 4, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein m is 0 or 1 and R^3 is halo.

6. A compound of the formula (1) as claimed in any one of the preceding claims, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy.

7. A compound of the formula (1) as claimed in any one of Claims 1 to 5, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein n is 0.

8. A compound of the formula (1) as claimed in any one of Claims 1 to 7, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein R^2 is selected from 1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(1-4C)alkyl, -(1-4C)alkylSO_2(1-4C)alkyl, hydroxy(1-4C)alkylSO_2(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO_2(1-4C)alkyl-.

9. A compound of the formula (1) as claimed in Claim8, or a pharmaceutically-acceptable salt or in-vivo hydrolysable ester thereof, wherein R^2 is selected from hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO_2(1-4C)alkyl.

10. A pharmaceutical composition which comprises a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1 in association with a pharmaceutically-acceptable diluent or carrier.

11. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use in a method of treatment of a warm-blooded animal such as man by therapy.

12. A compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, for use as a medicament.

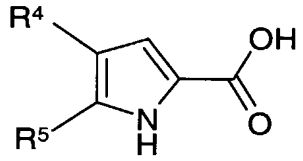
13. A compound of the formula (1), or a pharmaceutically acceptable salt or *in vivo* hydrolysable ester thereof, as claimed in claim 1, for use as a medicament in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

14. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes, insulin resistance, syndrome X, hyperinsulinaemia, hyperglucagonaemia, cardiac ischaemia or obesity in a warm-blooded animal such as man.

15. The use of a compound of the formula (1), or a pharmaceutically acceptable salt or in-vivo hydrolysable ester thereof, as claimed in claim 1, in the manufacture of a medicament for use in the treatment of type 2 diabetes in a warm-blooded animal such as man.

16. A process for the preparation of a compound of formula (1) as claimed in claim 1 (wherein R^1 to R^5 are as defined in claim 1), which process comprises:

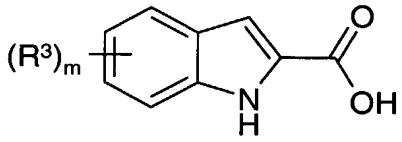
reacting an acid of the formula (3a):



(3a)

or an activated derivative thereof;

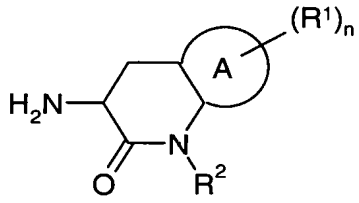
or an acid of the formula (3b)



(3b)

or an activated derivative thereof;

with an amine of formula (4):



(4)

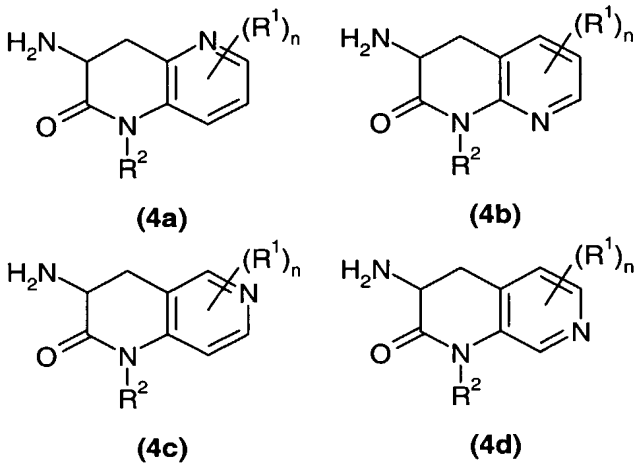
and thereafter if necessary:

i) converting a compound of the formula (1) into another compound of the formula (1);

ii) removing any protecting groups;

iii) forming a pharmaceutically acceptable salt or *in vivo* hydrolysable ester.

17. A compound of formula (4) as shown in Claim 16, which is a compound of formula (4a) , (4b), (4c) or (4d),



(4a) (4b) (4c) (4d)

wherein n is 0 or 1; either R^1 is a substituent at the 5-position of the pyridyl ring and is independently selected from halo, nitro, cyano, hydroxy, carboxy, carbamoyl, *N*-(1-4C)alkylcarbamoyl, *N*,*N*-((1-4C)alkyl)$_2$carbamoyl, sulphamoyl, *N*-(1-4C)alkylsulphamoyl, *N*,*N*-((1-4C)alkyl)$_2$sulphamoyl, -S(O)$_b$(1-4C)alkyl (wherein b is 0,1,or 2), -OS(O)$_2$(1-4C)alkyl, (1-4C)alkyl, (2-4C)alkenyl, (2-4C)alkynyl, (1-4C)alkoxy, (1-4C)alkanoyl, (1-4C)alkanoyloxy, hydroxy(1-4C)alkyl, fluoromethyl, difluoromethyl, trifluoromethyl, trifluoromethoxy and –NHSO$_2$(1-4C)alkyl;

or R^1 is a substituent at the 6-, 7- or 8-position of the pyridyl ring and is independently selected from halo, hydroxy, methyl and methoxy;

R^2 is selected from (1-4C)alkyl, cyano(1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO$_2$(1-4C)alkyl, hydroxy(1-4C)alkylSO$_2$(1-4C)alkyl-, (1-4C)alkoxy(1-4C)alkylSO$_2$(1-4C)alkyl-, –(1-4C)alkylNHSO$_2$(1-4C)alkyl, -(1-4C)alkylSO$_2$NH(1-4C)alkyl, -(1-4C)alkylSO$_2$Ndi[(1-4C)alkyl], -(1-4C)alkylCONH(1-4C)alkyl, -(1-4C)alkylCONdi[(1-4C)alkyl] and -(1-4C)alkylNHCO(1-4C)alkyl; provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then n ≠ 0.

18. A compound of the formula (4a), (4b), (4c) or (4d), as claimed in Claim 17, wherein n is 0 or 1; R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy; and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, (1-4C)alkoxy(1-4C)alkyl, hydroxy(1-4C)alkoxy(1-4C)alkyl, (1-4C)alkoxy(1-4C)alkoxy(1-4C)alkyl, di(1-4C)alkoxy(2-4C)alkyl, -(1-4C)alkylSO$_2$(1-4C)alkyl,

hydroxy(1-4C)alkylSO$_2$(1-4C)alkyl-, and (1-4C)alkoxy(1-4C)alkylSO$_2$(1-4C)alkyl-; provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then n ≠ 0.

19. A compound of the formula (4a), (4b), (4c) or (4d), as claimed in Claim 17 or Claim 18, wherein n is 0 or 1, R^1 is selected from fluoro, chloro, hydroxy, methyl and methoxy and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO$_2$(1-4C)alkyl; provided that, in a compound of formula (4a) or (4d), if n = 0 then R^2 is not hydrogen, and if R^2 is hydrogen then n ≠ 0.

20. A compound of the formula (4a), (4b), (4c) or (4d), as claimed in Claim 17, Claim 18 or Claim 19, wherein n is 0 and R^2 is selected from hydrogen, (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl, and -(1-4C)alkylSO$_2$(1-4C)alkyl; provided that, in a compound of formula (4a) or (4d) R^2 is not hydrogen.

21. A compound of the formula (4a), (4b), (4c) or (4d), as claimed in anyone of Claims 17 to 20, wherein n is 0.

22. A compound of the formula (4a), (4b), (4c) or (4d), as claimed in anyone of Claims 17 to 20, wherein R^2 is hydrogen.

23. The compound 3-amino-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one.

24. The compound 3-amino-3,4-dihydro-1,6-naphthyridin-2(1*H*)-one.

INTERNATIONAL SEARCH REPORT

PCT/GB2004/003648

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/407 C07D519/00 A61P3/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/20530 A (FREEMAN SUE ; KENNY PETER (GB); MORLEY ANDREW (GB); WHITTAMORE PAUL (G) 14 March 2002 (2002-03-14) page 36, line 25 - page 39, line 30; examples 120,144,146	1-24
Y	EP 1 136 071 A (PFIZER PROD INC) 26 September 2001 (2001-09-26) the whole document	1-24
P,X	WO 03/074532 A (BIRCH ALAN MARTIN ; MORLEY ANDREW DAVID (GB); WHITTAMORE PAUL ROBERT O) 12 September 2003 (2003-09-12) method 25-page 108 and method 28 page 110claims; examples 48,49	1-24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
21 October 2004	03/11/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

PCT/GB2004/003648

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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1

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Information on patent family members

PCT/GB2004/003648

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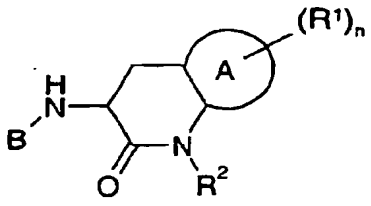
WO 03074532 A	12-09-2003	WO 03074532 A1	12-09-2003
WO 03074513 A	12-09-2003	WO 03074513 A2	12-09-2003

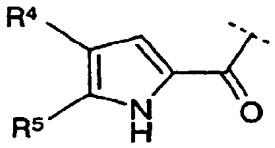
Box No. IV Text of the abstract (Continuation of item 5 of the first sheet)

Heterocyclic amides of formula (1)

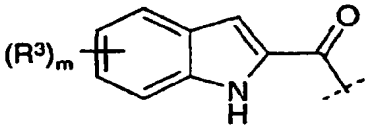


(1)

wherein: B is selected from



and



(2a) (2b)

~~R^3 is for example halo~~;

R^4 and R^5 together are either $-S-C(R^6)=C(R^7)-$ or $-C(R^7)=C(R^6)-S-$;

~~R^6 and R^7 are for example selected from hydrogen and halo~~.

A is a pyridylene ring;

m is 0, 1 or 2;

n is 0 or 1;

~~R^1 is for example independently selected from halo, hydroxy, methyl and methoxy~~

R^2 is for example selected from (1-4C)alkyl, hydroxy(1-4C)alkyl, dihydroxy(2-4C)alkyl and (1-4C)alkoxy(1-4C)alkyl.

or a pharmaceutically acceptable salt ~~or pro-drug thereof~~ possess glycogen phosphorylase inhibitory activity and accordingly have value in the treatment of disease states associated with increased glycogen phosphorylase activity. Processes for the manufacture of said heterocyclic amide derivatives, intermediates in said processes and pharmaceutical compositions containing the heterocyclic amide derivatives are described.